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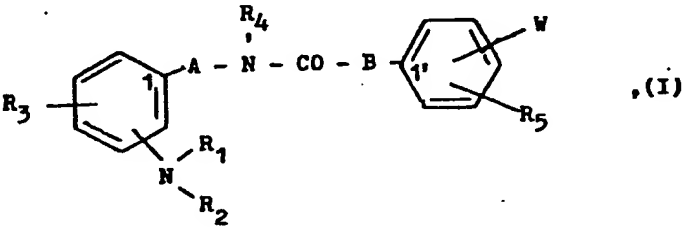
(57) Compounds of general formula I



,(I)

(wherein, in outline, R_1 and R_2 represent alkyl or cycloalkyl groups or together with the nitrogen atom to which they are attached, represent a cyclic imino group, R_3 represents a hydrogen or a halogen atom, an optionally substituted hydroxy, mercapto, amino, carboxy or aminocarbonyl group, or a nitro, alkanoyl, aminosulfonyl, alkyl, trifluoromethyl or cyano group, R_4 represents a hydrogen atom or an alkyl group, R_5 represents a hydrogen or a halogen atom or an alkyl group, A represents a bond or an optionally substituted methylene, ethylene, cycloalkylidene or vinylidene group, B represents a methylene or ethylene group optionally substituted by an alkyl group and W represents a hydrogen or a halogen atom, a cyano, alkanoyl or nitro group, an optionally substituted amino or aminocarbonyl group, a carboxy group, or an ester thereof, a formyl group or an acetal thereof or an optionally substituted alkyl or alkenyl group); and salts thereof formed with acids and bases. Processes for the preparation of the new compounds as well as pharmaceutical compositions containing them are also objects of this invention.

The new compounds show valuable pharmacutical properties, especially effects on intermediary metabolism and a blood-sugar lowering activity.

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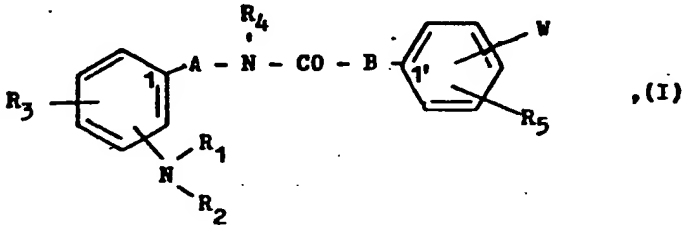
Certain of the chemical formulæ appearing in the printed specification were submitted after the date of filing, the formulæ originally submitted being incapable of being satisfactorily reproduced.

SPECIFICATION

Chemical compounds

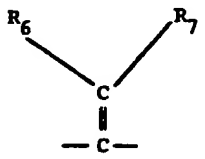
This invention relates to new carboxylic acid amides, to processes for their preparation and to pharmaceutical compositions containing them, and also to their use in the treatment of disorders of intermediary metabolism.

According to one feature of the present invention there are provided compounds of general formula I



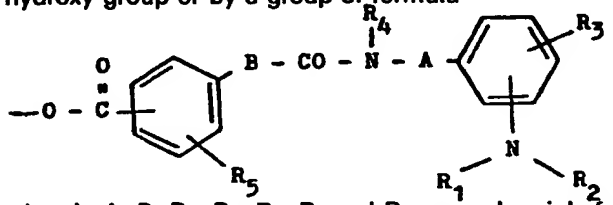
,(I)

[wherein R_1 and R_2, which may be the same or different, each represents an alkyl group containing 1 to 6 carbon atoms or a cycloalkyl group containing 5 to 7 carbon atoms, or R_1 and R_2 together with the nitrogen atom to which they are attached represent an unbranched alkyleneimino group containing 3 to 6 carbon atoms optionally substituted by 1 or 2 alkyl groups, each containing 1 to 3 carbon atoms, or by a hydroxy group and in which a methylene group may optionally be replaced by a carbonyl group, by an oxygen or sulfur atom or by an imino group (which may optionally be substituted by an alkyl group containing 1 to 3 carbon atom, an aralkyl group containing 7 to 10 carbon atoms or by a phenyl or halophenyl group) or an ethylene group may optionally be replaced by an O-phenylene group; and unbranched alkenyleneimino group containing 4 to 6 carbon atoms; a saturated or partly unsaturated azabicycloalkyl group containing 6 to 10 carbon atoms; an aza-1,4-dioxaspiro-alkyl group containing 6 to 8 carbon atoms; or a heptamethyleneimino, octamethyleneimino, nonamethyleneimino or decamethyleneimino group; R_3 represents a hydrogen or halogen atom, a trifluoromethyl, alkyl, hydroxy, alkoxy, alkanoyloxy, mercapto, alkylmercapto, nitro, amino, cyano, alkanoyl, carboxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminosulfonyl, alkylamino, dialkylamino, alkanoylamino, alkoxycarbonylamino or alkylsulfonylamino group (wherein each alkyl part in the above mentioned groups may contain from 1 to 3 carbon atoms), an aralkoxy group containing 7 to 10 carbon atoms or an arylcarbonylamino group; R_4 represents a hydrogen atom or an alkyl group containing 1 to 3 carbon atoms; R_5 represents a hydrogen atom, a halogen atom or an alkyl group containing 1 to 3 carbon atoms; A represents a bond, a methylene or ethylene group optionally substituted by an alkyl group containing 1 to 5 carbon atoms,ıa methylene or ethylene group substituted by two alkyl groups each containing 1 to 3 carbon atoms, a methylene group substituted by a cycloalkyl group containing 3 to 7 carbon atoms or by a hydroxyalkyl, alkoxyalkyl, cyano, carboxyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aryl or aralkyl group, wherein each of the alkyl parts may contain from 1 to 3 carbon atoms, a cycloalkylidene group containing 3 to 7 carbon atoms or a vinylidene group of formula



wherein R_6 and R_7, which may be the same or different, each represents a hydrogen atom or an alkyl group containing 1 to 3 carbon atoms or one of the radicals R_6 and R_7 represents a cycloalkyl group containing 3 to 7 carbon atoms or an aryl or aralkyl group and the other is as defined abov or R_6 and R_7 together with the carbon atom to which th y are attached, represent a cycloalkylidene radical containing 5 to 7 carbon atoms; B represents a methylene or ethylene group optionally substituted by an alkyl group containing 1 to 3 carbon atoms and W represents a hydrog n or halogen atom, a nitro group, an amino group (optionally substituted by an alkanoyl group containing 1 to 3 carbon atoms) an alkyl group containing 1 to 3 carbon atoms (optionally substitut d by a hydroxy or carboxy group or by one or two alkoxycarbonyl groups containing 2 to 4 carbon atoms each), an alkenyl group containing 2 to 5 carbon atoms substitut d by a carboxy or alkoxycarbonyl group containing 2 t 4 carbon atoms, an alkanoyl

group containing 1 to 3 carbon atoms, a dialkoxymethyl or trialkoxymethyl group containing 1 to 3 carbon atoms in each alkyl part, an alkylenedioxymethyl group containing 2 or 3 carbon atoms in the alkylene part, a 1,3-oxazoline-2-yl or cyano group, an aminocarbonyl group (optionally substituted by on or two alkyl groups containing 1 to 4 carbon atoms in each alkyl part), an unbranched alkyleneiminocarbonyl group containing 5 to 8 carbon atoms a morpholinocarbonyl group, a (dialkyldioxolane-yl)-alkoxycarbonyl group containing 7 to 10 carbon atoms or a carboxy group or esterfied carboxy group wherein if the said ester group consists of an alkyl group containing 1 to 6 carbon atoms this may be substituted, in any but the α-position, by a hydroxy, alkoxy, amino, alkylamino, dialkylamino, 1,3-dimethylxanthine-7-yl, alkanoyloxy, aroyloxy, aralkanoyloxy or pyridine-carbonyloxy group or by two hydroxy groups—except in the case of any methyl or methylene group in the above cases, which can only be substituted by one hydroxy group or by a group of formula



wherein A, B, R_1, R_2, R_3, R_4 and R_5 are as hereinbefore defined whereby each alkyl part of the above alkyl ester substituents may contain from 1 to 3 carbon atoms), and salts thereof.

The new compounds possess interesting pharmacological properties, especially in general an ffect an intermediary metabolism and in particular a blood-sugar lowering activity.

For pharmaceutical use, the salts referred to above will of course be physiologically compatible salts formed with acids or bases, but other salts may find use in the preparation of the compounds of formula I and their physiologically compatible salts. The term "salts formed with acids or bases" includes salts formed with inorganic or organic acids or bases.

The invention extends to all possible isomers, including optional isomers, of compounds of formula I. R_1 and R_2 together with the nitrogen atom may represent for example, dimethylamino, diethylamino, dipropylamino, dibutylamino diisobutylamino, dipentylamino, dihexylamino, N-methyl-N-ethylamino, N-methyl-N-propylamino, N-isopropyl-N-propylamino, N-isobutyl-N-propylamino, N-methyl-N-isopropylamino, N-methyl-N-butylamino, N-ethyl-N-butylamino, N-ethyl-N-isopropylamino, N-ethyl-N-pentylamino, N-propyl-N-butylamino, N-methyl-N-cyclopentylamino, N-ethyl-N-cyclopentylamino, N-methyl-N-cyclohexylamino, N-ethyl-N-cyclohexylamino, N-propyl-N-cyclohexylamino, N-isobutyl-N-cyclohexylamino, pyrrolidino, piperidino, hexamethyleneimino, heptamethyleneimino, octamethylenimino, nonamethyleneimino, decamethyleneimino, dimethylazetidino, methyl-pyrrolidino, dimethyl-pyrrolidino, ethyl-pyrrolidino, methyl-piperidino, dimethyl-piperidino, ethyl-piperidino, diethyl-piperidino, methyl-ethyl-piperidino, propyl-piperidino, methyl-propyl-piperidino, isopropyl-piperidino, cis-3,5-dimethyl-piperidino, trans-3,5-dimethyl-piperidino, morpholino, thiomorpholino, piperazino, N-methyl-piperazino, N-ethyl-piperazino, N-propyl-piperazino, N-isopropyl-piperazino, N-benzylpiperazino, N-(2-phenyl)ethyl)-piperazino, N-(3-phenylpropyl)-piperazino, N-phenyl-piperazino, N-fluorophenylpiperazino, N-chlorophenyl-piperazino, N-bromophenyl-piperazino, hydroxy-pyrrolidino, hydroxy-piperidino, hydroxy-hexamethyleneimino, pyrrolidone-1-yl, piperidone-1-yl, hexahydroazepinone-1-yl, tetrahydro-isoquinoline-2-yl, octahydro-isoquinoline-2-yl, decahydro-isoquinoline-2-yl, dihydro-isoindole-2-yl, hexahydro-isoindole-2-yl, octahydro-isoindole-2-yl, tetrahydro-3-benzazepine-3-yl, decahydro-3-benzazepine-3-yl, 3-aza-bicyco[3.2.0]heptane-3-yl, 3-aza-bicyclo[3.2.1]octane-3-yl, 3-aza-bicyclo[3.3.2]nonane-3-yl, 1,4-dioxa-7-aza-spiro[4,4]nonane-7-yl, 1,4-dioxa-7-azaspiro[4,5]decane-7-yl, 1,4-dioxa-8-aza-spiro[4,5]decane-8-yl, 1,4-dioxa-8-aza-spiro[4,6]undecane-8-yl, pyrrolino or tetrahydropyridine group;

R_3 may represent, for example, a hydrogen, fluorine, chlorine, bromine or iodine atom, or a methyl, ethyl, propyl, isopropyl, hydroxy, methoxy, ethoxy, propoxy, isopropoxy, acetoxy, propionyloxy, mercapto, methylmercapto, ethylmercapto, propylmercapto, isopropylmercapto, trifluoromethyl, nitro, cyano, formyl, acetyl, propionyl, aminosulfonyl, amino, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, dipropylamino, diisopropylamino, N-methyl-N-ethyl-amino, N-methyl-N-isopropylamino, N-ethyl-N-propylamino, formylamino, acetylamino, propionylamino, methylsulfonylamino, ethylsulfonylamino, propylsulfonylamino, isopropylsulfonylamino, carboxy, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, isopropoxycarbonylamino, benzoylamino, benzyloxy, 1-phenylethoxy, 2-phenyl-ethoxy, 3-phenyl-propoxy, aminocarbonyl, methylaminocarbonyl, ethylaminocarbonyl, isopropylaminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, methyl-ethylaminocarbonyl, or methyl-propylaminocarbonyl group;

R_4 may represent a hydrogen atom, or a methyl, ethyl, propyl or an isopropyl group;

R_5 may represent a hydrogen, fluorin , chlorine, bromin or an iodine atom, or a m thyl,

ethyl, propyl or an isopropyl group;

A may represent, for xample, a single bond, or a methylene, thylidene, ethyl-methylene propyl-methylene, isopropyl-methyl ne, butyl-m thylene, pentyl-methyl ne, dim thyl-methylene, diethyl-methylen , dipropyl-methylene, methyl-ethylmethylene, methyl-propyl-methylene, ethyl-propyl-methylene, ethyl-isopropyl-methylene, ethylene, methylethylene, ethyl-ethylene, propyl-ethylene, dimethylethylene, cyclopropyl-methylene, cyclobutyl-methylene, cyclopentyl-methylene, cyclohexyl-methylene, cycloheptyl-methylene, cyclopropylidene, cyclobutylidene, cyclopentylidene, cyclohexylidene, cycloheptylidene, carboxymethylene, methoxycarbonyl-methylene, ethoxycarbonyl-methylene, propoxycarbonyl-methylene, hydroxymethyl-methylene, 1-hydroxyethyl-methylene, 2-hydroxyethyl-methylene, 1-hydroxypropyl-methylene, 3-hydroxypropyl-methylene, methoxymethylmethylene, ethoxymethyl-methylene, propoxymethyl-methylene, 1-methoxyethyl-methylene, 2-methoxyethyl-methylene, 2-ethoxyethyl-methylene, cyano-methylene, aminocarbonylmethylene, methylaminocarbonyl-methylene, dimethylaminocarbonyl-methylene, ethylaminocarbonyl-methylene, diethylaminocarbonyl-methylene, propylaminocarbonyl-methylene, phenyl-methylene, benzyl-methylene, 1-phenylethyl-methylene, 2-phenylethyl-methylene, 3-phenylpropyl-methylene, 2-phenylpropyl-methylene, vinylidene, methyl-vinylidene, dimethyl-vinylidene, ethyl-vinylidene, diethyl-vinylidene, propyl-vinylidene, dipropyl-vinylidene, ethyl-methyl-vinylidene, ethyl-propyl-vinylidene, methylpropyl-vinylidene, cyclopentyl-vinylidene, cyclohexyl-vinylidene, phenyl-vinylidene, benzyl-vinylidene, 2-phenethyl-vinylidene, cyclopropylidene-methylene, cyclopentylidene-methylene, cyclohexylidene-methylene or cycloheptylidene-methylene group;

B may represent, for example, a methylene, ethylene, ethylidene, propyl-methylene or isopropyl-methylene group; and W may represent, for example, a hydrogen, chlorine, bromine or iodine atom, or a methyl, ethyl, propyl, isopropyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 3-hydroxypropyl, carboxymethyl, 1-carboxyethyl, 2-carboxyethyl, 3-carboxy-propyl, methoxycarbonyl-methyl, ethoxycarbonyl-methyl, propoxycarbonyl-methyl, 2-methoxycarbonyl-ethyl, 2-ethoxycarbonyl-ethyl, 3-ethoxycarbonylpropyl, bis-(methoxycarbonyl)-methyl, bis-(ethoxycarbonyl)-methyl, 2,2-bis-(ethoxycarbonyl)-ethyl, carboxyl-vinyl, carboxy-propenyl, carboxy-pentenyl, methoxycarbonyl-vinyl, ethoxycarbonyl-vinyl, propoxycarbonyl-vinyl, formyl, acetyl, propionyl, dimethoxymethyl, diethoxy-methyl, dipropoxy-methyl, trimethoxymethyl, triethoxy-methyl, 1,2-ethylenedioxy-methyl, 1,3-propylenedioxy-methyl, cyano, nitro, amino, formylamino, acetamino, propionylamino, 1,3-oxazoline-2-yl, aminocarbonyl, methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, isopropylaminocarbonyl, butylaminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, dibutylaminocarbonyl, pyrrolidinocarbonyl, piperidinocarbonyl, hexamethyleneininocarbonyl, heptamethyleneiminocarbonyl, morpholinocarbonyl, carboxy, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert.butoxycarbonyl, pentoxycarbonyl, hexoxycarbonyl, heptoxycarbonyl, octoxycarbonyl, allyloxycarbonyl, butenyloxycarbonyl, benzyloxycarbonyl, 1-phenylethoxycarbonyl, 2-phenylethoxycarbonyl, 3-phenylpropoxycarbonyl, 2-hydroxyethoxycarbonyl, 2-hydroxypropoxycarbonyl, 3-hydroxypropoxycarbonyl, 2-methoxyethoxycarbonyl, 2-ethoxyethoxycarbonyl, (2,2-dimethyl-dioxolane-4-yl)-methoxycarbonyl, 2-(2,2-dimethyl-dioxolane-4-yl)-ethoxycarbonyl, (2,2-diethyl-dioxolane-4-yl)-methoxy-carbonyl, 2-(2,2-diethyl-dioxolan-4-yl)-ethoxycarbonyl, 3-(2,2-dimethyl-dioxolane-4-yl)-propoxycarbonyl, 2-aminoethoxycarbonyl, 2-dimethylaminoethoxycarbonyl, 2-diethylamino-ethoxycarbonyl, 2-(1,3-dimethyl-xanthine-7-yl)-ethoxycarbonyl, 2-acetoxy-ethoxycarbonyl, 2-benzyloxy-ethoxycarbonyl, 2-phenylacetoxyethoxycarbonyl, 2-pyridinecarbonyloxy-ethoxycarbonyl, 2,3-dihydroxy-propoxycarbonyl, 3,4-dihydroxy-butoxycarbonyl, 2-[4-[(1,(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoyloxy]ethoxycarbonyl or 3-[4-[(1-(2-piperidino-pheyl)-ethyl)-aminocarbonylmethyl]-benzoyloxy]propoxycarbonyl group.

Preferred compounds of the above general formula I are, however, those wherein R_1 and R_2 together with nitrogen atom to which they are attached represent a dialkylamino or N-alkyl-cyclohexylamino group, wherein each alkyl part may contain from 1 to 4 carbon atoms, an unbranched alkyleneimino group containing 3 to 6 carbon atoms (optionally substituted by one or two methyl groups), a hydroxypiperidino, piperidone-1-yl, tetrahydro-pyridino, morpholino, thiomorpholino, N-methylpiperazino, N-benzylpiperazino, N-chlorophenyl-piperazino, heptamethyleneimino or octamethyleneimino group, a saturated or partly unsaturated azabicycloalkyl group containing 7 to 9 carbon atoms, an unbranched alkyleneimino group containing 4 to 6 carbon atoms wherein one ethylene group is replaced by a o-phenylene group, or a 1,4-dioxa-aza-spiro-alkyl group containing 7 or 8 carbon atoms;

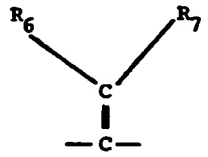
R_3 represents a hydrogen, fluorine, chlorine, bromine or iodine atom, or a methyl, trifluoromethyl, hydroxy, methoxy, benzyloxy, acetoxy, mercapto, m thylmercapto, nitro, amino dimethylamino, acetylamin , methylsulfonylamino, benzoylamino, ethoxy-carbonylamino, cyano, carb xy, methoxycarbonyl, ethoxycarbonyl, aminocarbonyl, acetyl or aminosulfonyl group;

R_4 repr sents a hydrog n atom or a methyl group;

R_5 represents a hydrogen atom, a chlorine atom or a methyl group;

A repres nts a bond, or a methylene group (optionally substituted by an alkyl group

containing 1 t 3 carbon atoms, or by a phenyl, cyclohexyl, carboxy, meth xycarbonyl or a hydroxymethyl group), a dimethyl-m thylene, cyclopropylidene or ethylene group or a vinylidene group of formula

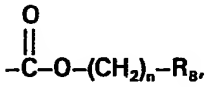


wherein R_6 and R_7, which may be the same or different, each represents a hydrogen atom or a methyl group or R_6 and

R_7 together with the carbon atom to which they are attached represent a cycloalkylidene radical containing 1 to 3 carbon atoms:

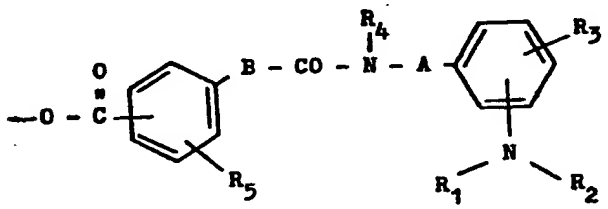
B represents a methylene, ethylidene or ethylene group; and

W represents a hydrogen atom, or a methyl, ethyl, hydroxymethyl, cyano or carboxyvinylene group, an alkyl group containing 1 to 3 carbon atoms substituted by a carboxy group or by one or two alkoxycarbonyl groups containing 2 to 4 carbon atoms each, a carbonyl group (substituted by a hydrogen atom, a methyl, ethyl, hydroxy alkoxy, (2,2-dimethyl-dioxolane-4-yl)-methoxy, benzyloxy, pyridyl-methyoxy, amino, alkylamino, dialkylamino, piperidino or morpholino group), whereby any alkyl part in the aforementioned groups may contain from 1 to 3 carbon atoms, or a group of formula

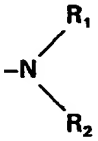


wherein n is 2, 3, or 4; and

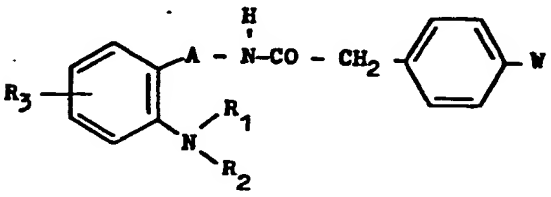
R_8 represents a hydroxy, methoxy, ethoxy, acetoxy, benzoyloxy, pyridinecarbonyloxy group, a dialkylamino group containing 1 to 3 carbon atoms in each alkyl part, 1 1,3-dimethylxanthiene-7-yl group of a group of formula



wherein A, B, R_1, R_2, R_3, R_4 and R_5 are as hereinbefore defined; and especially those compounds of general formula I wherein the radical



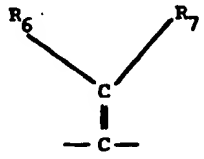
is in the 2-position and the radical W is in the 4'-position. Especially preferred are compounds f general formula Ia



,(Ia)

wherein R_1 and R_2 together with the nitrog n atom to which they are attached, represent a dimethylamino, pyrrolidino, methylpyrrolidino, piperidino, methylpiperidino, dimethylpiperidino, tetrahydro-pyridino, 2-octahydroisoindolo r hexamethyleneimino group; R_3 represents a hydrogen, fluorine or a chlorine atom or a methyl group;

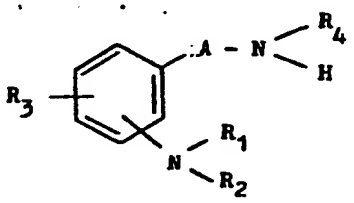
A represents a methylene group (optionally substituted by a cyclohexyl, phenyl, m thoxycarbonyl, ethoxycarbonyl or an alkyl group containing 1 to 3 carbon atoms), or a dimethylmethylene group or a vinyliden group of formula



wherein R_6 and R_7 each represents a hydrogen atom or together with the carbon atom to which they are attached represent a cyclohexylidene group; and W represents a methyl, hydroxymethyl or a carboxymethyl group, or a carbonyl group (substituted by a hydrogen atom, a methyl, hydroxy, methoxy, ethoxy, propoxy, isopropoxy, 2-hydroxyethoxy, 2-methoxyethoxy, (2,2-dimethyl-dioxolane-4-yl)-methoxy, or a 2-diethylaminoethoxy group).

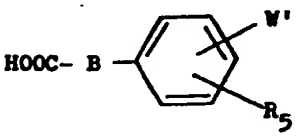
The compounds of formula I may, for example, be prepared by the following processes, which processes constitute further features of the present invention:

(a) Acylation of an amine of general formula II



,(II)

wherein A, R_1, R_2, R_3 and R_4 are as hereinbefore defined, (or if A represents one of the above mentioned vinylidene groups one of its tautomers, or its lithium or magnesium halide complex) with a carboxylic acid of general formula III



,(III)

wherein R_5 and B are as hereinbefore defined and W' represents W as hereinbefore defined or represents a carboxyl group protected by a protective radical, or with reactive derivatives thereof optionally prepared in the reaction mixture.

Suitable reactive derivatives of a compound of general formula III includes, for example, ester (such as the methyl, ethyl or benzyl ester), thioesters (such as the methylthio or ethylthioester), halides (such as the acid chloride), anhydrides or imidazolides thereof. The reaction is conveniently carried out in a solvent, such as for example methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxan, benzene, toluene, acetonitrile or dimethylformamide, optionally in the presence of an acid-activating or a dehydrating agent, (e.g. in the presence of ethyl chloroformate, thionyl chloride, phosphorous trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N-dicyclohexylcarbodiimide/N-hydroxy-succinimide, N,N'-carbonyldiimidazole, N,N'-thionyldiimidazole, or triphenyl phosphine/carbon tetrachloride), or of an agent activating the amino group (e.g. phosphorous chloride) and optionally in the presence of an inorganic base such as, for example, sodium carbonate or a tertiary organic base such as triethyl-amine or pyridine, which simultaneously may serve as a solvent, at temperatures between −25 and 250°C, preferably, however, at temperatures between −10°C and the boiling temperature of the used solvent. The reaction may also be carried out without a solvent. Furthermore, the water which is formed during the reaction may be removed by azeotropic distillation (e.g. by heating with toluene in a water separator funnel) or by addition of a drying agent such as magnesium sulfate or a molecular sieve.

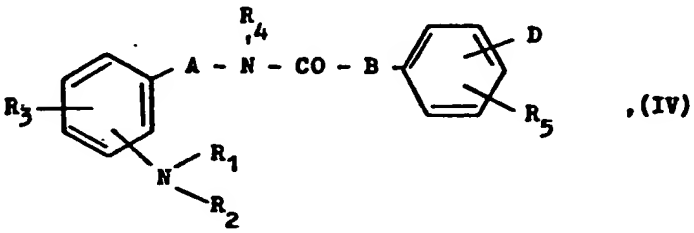
If necessary, the subsequent removal of a protective radical is preferably carried out hydrolytically, conveniently in the presence of either an acid (such as, for example, hydrochloric, sulfuric, phosphoric or trichloroacetic acid) or a base such as sodium hydroxide or potassium hydroxid in a solvent such as for example water, methanol, ethanol, ethanol/water, water/isopropanol or water/dioxan at temperatures between −10 and 120°C, e.g. at temperatures between room temperature and the boiling temperature of the reaction mixture. A tert.butyl radical used as protective radical may also be removed thermolytically (optionally in an inert solvent such as methylene choride, chloroform, benzene, toluene, trahydrofuran or dioxan) and preferably in the presence of a catalytic amount of an acid such as, for example, p-toluenesulfonic, sulfuric, phosphoric or polyphosphoric acid.

Furthermore, a benzyl radical used as protective radical may also be removed hydrogenolyti-

cally (in the presence of a hydrogenation catalyst such as palladium/charcoal) in a solvent such as, for example, methanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxan or dimethyl formamide.

(b) For the preparation of compounds of general formula I, wherein W represents a carboxy group:

Cleavage of a compound of general formula IV



,(IV)

wherein R_1, R_2, R_3, R_5, A and B are defined as mentioned before and D represents a group which may be converted into a carboxy group by means of hydrolysis, thermolysis or hydrogenolysis.

Suitable hydrolysable groups include, for example, carboxy derivatives (such as unsubstituted or substituted amides, esters, thioesters, orthoesters, iminoethers, amidines or anhydrides), a nitrile group, a malonic ester-(1)-yl group, a tetrazolyl group or an optionally substituted 1,3-oxazole-2-yl or 1,3-oxazoline-2-yl group.

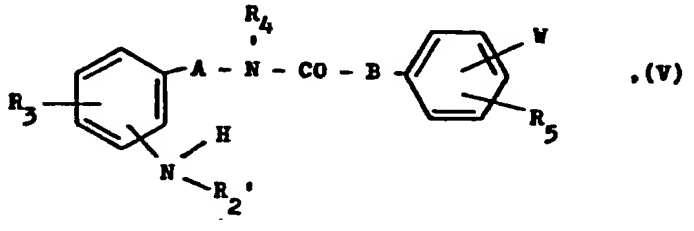
Suitable thermolytically cleavable groups include, for example, esters with tertiary alcohols, e.g. the tert.butyl ester.

Suitable hydrogenolytically cleavable groups include, for example, aralkyl groups, e.g. the benzyl group.

The hydrolysis is conveniently carried out either in the presence of an acid (such as for example, hydrochloric, sulfuric, phosphoric or trichloroacetic acid) or a base (such as sodium hydroxide or potassium hydroxide) in a solvent such as, for example, water/methanol, ethanol, water/ethanol, water/isopropanol or water/dioxan at temperatures between −10 and 120°C, e.g. at temperatures between room temperature and the boiling temperature of the reaction mixture.

Thus if, for example, D in a compound of general formula IV represents a nitrile or aminocarbonyl group, these groups may be converted into a carboxy group with a nitrite, e.g. sodium nitrite, in the presence of an acid (such as sulfuric acid), whereby conveniently this acid is simultaneously used as a solvent, at temperatures between 0 and 50°C; if for example, D represents a tert.butyloxycarbonyl group, the tert.butyl group may be split off thermolytically (optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxan) and preferably in the presence of a catalytic amount of an acid such as p-toluenesulfonic, sulfuric, phosphoric or polyphosphoric acid preferably at the boiling temperature of the used solvent, e.g. at temperatures between 40 and 100°C; or if for example D represents a benzyloxycarbonyl group, the benzyl group may be split off hydrogenolytically in the presence of a hydrogenation catalyst such as palladium/charcoal in a solvent such as for example, methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxan or dimethyl formamide preferably at temperatures between 0 and 50°C, e.g. at room temperature, and at a hydrogen pressure of 1 to 5 bar. During the hydrogenolysis other groups may optionally simultaneously be reduced, e.g. a halogen compound may be dehalogenated, a nitro group may be converted into the corresponding amino group, or a vinylidene group into the corresponding alkylidene group.

(c) Reaction of a compound, optionally formed in the reaction mixture, of general formula V



,(V)

wherein R_3, R_4, R_5, A, B, and W are as hereinbefore defined and, R_2' represents a hydrogen atom or has the meanings mentioned before for R_2, with a compound of general formula VI

R_1'–E (VI)

[wherein R_1' has the meanings mentioned before for R_1 or together with the radical R_2' of formula V represents a straight-chained alkylene group containing 4 to 6 carbon atoms (optionally substituted by one or two alkyl groups containing 1 to 3 carbon atoms) or an n-pentylene group in which the third methylene group is replaced by an oxygen or sulfur atom, and E represents a nucleophilically exchangeable group such as a halogen atom or a sulfonyloxy group (e.g. a chlorine, bromine or an iodine atom or a methanesulfonyloxy or p-toluenesulfonyloxy group), or also a hydrogen atom if in R_1' one methylene group is replaced by an aldehyde or ketone carbonyl group], if necessary in the presence of a reducing agent, and optional subsequent hydrolysis.

Suitable alkylating agents of formula VI include, for example, the corresponding halides or sulfates such as methyl iodide, ethyl iodide, propyl bromide, dimethyl sulfate or diethyl sulfate.

The reaction is conveniently carried out in a solvent such as, for example, acetone, tetrahydrofuran, dimethyl formamide, dimethylsulfoxide or hexamethyl phosphoric acid triamide, optionally in the presence of an inorganic base (such as sodium carbonate, potassium carbonate or potassium tert.butylate) or tertiary organic base (such as pyridine) at temperatures between 0 and 150°C; preferably, however, at temperatures between 20 and 75°C. If a compound of general formula V is used wherein W represents a carboxyl group, this carboxyl group may simultaneously be converted into the corresponding ester depending on the reaction conditions, e.g. at temperatures above room temperature and in the presence of a base, for example sodium carbonate.

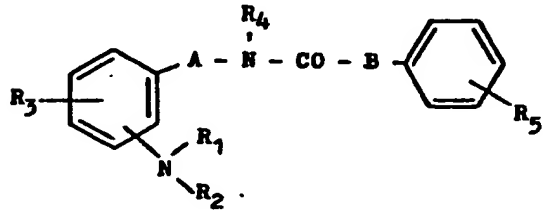
The methylation may optionally also be carried out so that a compound of general formula V is reacted with formalin in the presence of a reducing agent, e.g. formic acid or hydrogen in the presence of a hydrogenation catalyst (e.g. palladium or platinum), optionally in a solvent such as formic acid or glacial acetic acid at temperatures up to the boiling temperatures of the reaction mixture.

Moreover, the alkylation may optionally also be carried out with a corresponding carbonyl compound in the presence of a hydride such as sodium cyanoborohydride in a solvent such as for example acetonitrile/glacial acetic acid or dimethyl formamide/acetic acid preferably at pH 7 and at temperatures between 0 and 50°C.

The subsequent hydrolysis is preferably carried out in an aqueous solvent such as water/-methanol, water/ethanol or water/dioxan in the presence of an acid (such as hydrochloric or sulfuric acid) or a base (such as sodium or potassium hydroxide) at temperatures between 50 and 100°C.

(d) For the preparation of compounds of general formula I wherein W represents a carboxy group, an alkanoyl group containing 1 to 3 carbon atoms or an alkyl group containing 1 to 3 carbon atoms:

Reaction of a compound of general formula VII



(VII)

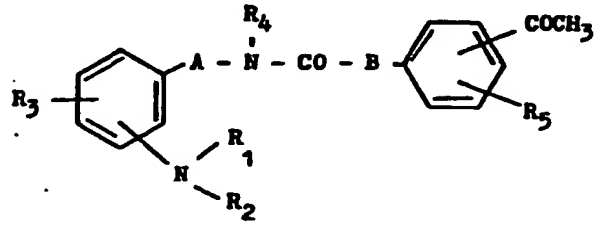
wherein R_1, R_2, R_3, R_4, R_5, A and B are as hereinbefore defined, with phosgene, an oxalyl halide, an alky or alkanoyl halide containing 1 to 3 carbon atoms in the alkyl part or with hydrogen cyanide and a hydrogen halide (preferably hydrogen chloride), in the presence of a Lewis acid.

Suitable halides include chlorides and bromides, and the Lewis acid is preferably aluminium chloride.

The reaction is preferably carried out in a solvent such as methylene chloride, nitrobenzene, chlorobenzene, dichlorobenzene, tetrachloroethane or carbon disulfide or in polyphosphoric acid at temperatures between 0 and 120°C, preferably, however at temperatures between 20 and 80°C. If in a compound of general formula VII, R_3 represents a hydrogen atom, this may simultaneously be replaced by a corresponding alkyl or acyl radical.

(e) For the preparation of compounds of general formula I wherein w represents a carboxy group;

Reaction of a compound of general formula VIII

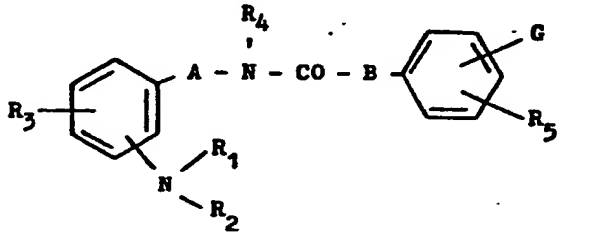


,(VIII)

wherein R_1, R_2, R_3, R_4, R_5, A and B are as hereinbefore defined, with a hypohalide optionally prepared in the reaction mixture. The reaction is conveniently carried out in a solvent (such as for example water/tetrahydrofuran or water/dioxan) and in the presence of a base (such as sodium hydroxide or potassium hydroxide) at temperatures between 0 and 80°C; preferably, however, at temperatures between 25 and 50°C.

(f) For the preparation of compounds of general formula I wherein W represents a carboxy group:

Oxidation of compound of general formula IX



,(IX)

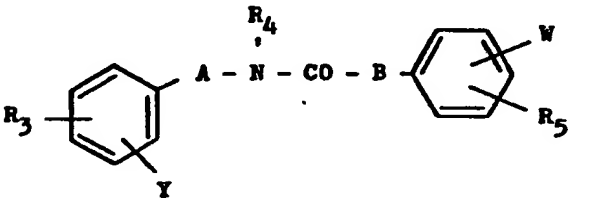
wherein R_1, R_2, R_3, R_4, R_5, A and B are as hereinbefore defined and G represents a group which may be converted by means of oxidation into a carboxy group.

Such an oxidizable group includes for example a formyl group or one of its acetals, a hydroxymethyl group or one of its ethers, or an unsubstituted or substituted acyl group (such as an acetyl, chloroacetyl, propionyl, malonic acid-(1)-yl group or a malonic ester-(1)-yl group).

The reaction is carried out by means of an oxidizing agent in a solvent (such as for example water, glacial acetic acid, pyridine or carbon tetrachloride) at temperature between 0 and 100°C, conveniently, however, at temperatures between 20 and 50°C. The reaction is preferably carried out with silver oxide/sodium hydroxide solution, manganese dioxide/acetone or methylene chloride, hydrogen peroxide/sodium hydroxide solution, bromine or chlorine/sodium or potassium hydroxide solution or chromium trioxide/pyridine.

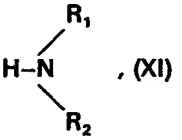
(g) For the preparation of compounds of general formula I, wherein R_3 represents a nitro group:

Reaction of a compound of general formula X



,(X)

(wherein R_4, R_5, A, B and W are as hereinbefore defined, R_3 represents a nitro group and Y represents a nucleophilically exchangeable radical such as a halogen atom) with an amine of general formula XI



, (XI)

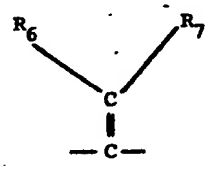
(wherein R_1 and R_2 are defined as mentioned before), and optional subsequent hydrolysis.

The term "a halogen atom" used in the definition of the exchangeable radical Y particularly represents a fluorine, chlorine or a bromine atom, and preferably in the o- or p-position relative to the nitro group.

The reaction is conveniently carried out in a solvent such as for example, water, water/methanol, water/ethanol, water/isopropanol, water/dioxan, methanol, ethanol, dimethyl formamide, or in an excess of the amine of general formula XI and/or the N-formyl derivative thereof (optionally in the presence of an inorganic or tertiary organic base), optionally in the presence of a reaction accelerator such as copper or a copper salt and optionally in a closed vessel at temperatures between 20 and 150°C; preferably, however at the boiling temperature of the reaction mixture (e.g. at 100°C). The reaction may, however, be carried out without a solvent.

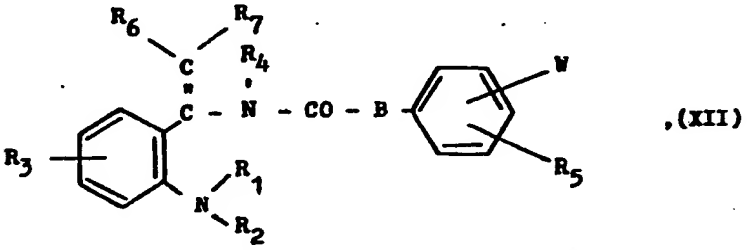
The optional subsequent hydrolysis is conveniently carried out in an aqueous solvent such as for example methanol/water, ethanol/water or dioxan/water in the presence of an acid (such as hydrochloric or sulfuric acid) or a base such as sodium or potassium hydroxide at temperatures between 50 and 100°C.

(h) For the preparation of compounds of general formula I, wherein A represents a group of formula



wherein R_6 and R_7 are as hereinbefore defined:

Reduction of an enamide of general formula XII



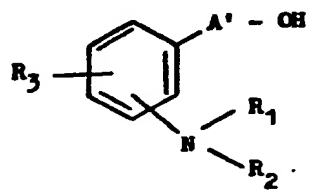
,(XII)

wherein R_1, R_2, R_3, R_5, R_6, R_7, B and W are as hereinbefore defined.

The reduction is preferably carried out with hydrogen in the presence of a hydrogenation catalyst such as palladium/charcoal or platinum in a solvent such as for example methanol, ethanol, isopropanol, ethanol/water glacial acetic acid, ethyl acetate, dioxan, tetrahydrofuran, dimethyl formamide, benzene, or benzene/ethanol at temperatures between 0 and 100°C, preferably, however at temperatures between 20 and 50°C, and a hydrogen pressure of 1 to 5 bar. When using a chiral hydrogenation catalyst such as a transition metal π-complex, e.g. a complex made from rhodium chloride and (+) or (−) 0,0-isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphino)-butane (= DIOP), the hydrogenation is effected enantioselectively. Moreover, other reduceable groups may be reduced during the catalytic hydrogenationm e.g. a nitro group to an amino group or a chlorine or a bromine atom to a hydrogen atom.

(i) For the preparation of compounds of general formula I, wherein R_4 represents a hydrogen atom and A represents a methylene or ethylene group (optionally substituted by an alkyl group containing 1 to 5 carbon atoms), a methylene or ethylene group substituted by two alkyl groups containing 1 to 3 carbon atoms each, a methyl group (substituted by a cycloalkyl group containing 3 to 7 carbon atoms, by an alkoxyalkyl, carboxyl, alkoxycarbonyl, aryl or an aralkyl group, whereby each of the aforementioned alkyl parts may contain from 1 to 3 carbon atoms), or a cycloalkylidene group 4 to 7 carbon atoms:

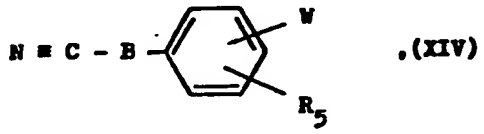
Reaction of a compound of general formula XIII



,(XIII)

[wherein R_1, R_2 and R_3 are as hereinbefore defined and A′ represents a methyl or thylen group (optionally substituted by an alkyl group containing 1 to 5 carbon atoms), a methylen or ethylene group substitut d by two alkyl groups containing 1 t 3 carbon atoms each, a methylene gr up (substituted by a cycloalkyl group containing 3 to 7 carbon atoms, an

alkoxyalkyl, carboxyl, alkoxycarbonyl, aryl, or an aralkyl group, whereby each of the above mentioned alkyl parts may contain from 1 to 3 carbon atoms), or a cycloalkylidene group containing 4 to 7 carbon atoms], with a compound of general formula XIV



.(XIV)

wherein R_5, B and W are as hereinbefore defined.

The reaction is carried out in the presence of a strong acid, which simultaneously may serve as solvent, preferably in concentrated sulfuric acid, at temperatures between 20 and 150°C, preferably at temperatures between 80 and 100°C.

According to a further feature of the present invention, a compound of general formula I thus obtained wherein W represents the carboxy group, may if desired, subsequently be converted into a corresponding compound of general formula I wherein W represents an ester or amide group by esterification or amidation and/or a compound of general formula I wherein R_3 and/or W represent(s) a nitro group, may subsequently be converted by reduction into a corresponding compound of general formula I wherein R_3 and/or W represent(s) an amino group; and/or a compound of general formula I wherein R_3 and/or W represent(s) amino group, may subsequently be converted via a corresponding diazonium salt into a corresponding compound of general formula I wherein R_3 represents a hydrogen or a halogen atom, a hydroxy, alkoxy, mercapto, alkylmercapto, chlorosulfonyl, or cyano group and/or W represents a hydrogen or a halogen atom or a cyano group. Optionally a compound of general formula I thus obtained, wherein R_3 represents a hydroxy group, may subsequently be converted by alkylation into a corresponding compound of general formula I wherein R_3 represents an alkoxy group, or a compound of formula I thus obtained, wherein R_3 represents a chlorosulfonyl group, may subsequently be converted by ammonia into a corresponding compound of general formula I wherein R_3 represents an aminosulfonyl group; and/or a compound of general formula I wherein R_3 represents an amino group may subsequently be converted by means of acylation into a corresponding compound of general formula I wherein R_3 represents an alkanoylamino, aroylamino, alkoxycarbonylamino or an alkylsulfonylamino group; and/or a compound of general formula I wherein R_3 represents an amino may subsequently be converted by means of alkylation into a corresponding compound of general formula I wherein R_3 represents an alkylamino or a dialkylamino group; and/or a compound of general formula I wherein R_3 represents a chlorine or a bromine atom may subsequently converted by means of dehalogenation into a corresponding compound of general formula I wherein R_3 represents a hydrogen atom; and/or a compound of general formula I wherein R_3 represents a nitrile group may subsequently be converted by means of hydrolysis or alcoholysis into a corresponding compound of general formula I, wherein R_3 represents an aminocarbonyl, carboxy or an alkoxycarbonyl group; and/or a compound of general formula I wherein R_3 represents a carboxy or alkoxycarbonyl group and/or W represents an (optionally esterified) carboxy group may subsequently be converted by means of reduction into a corresponding compound of general formula I wherein R_3 and/or W represents a formyl or hydroxymethyl group; and/or a compound of general formula I wherein W represents an alkoxycarbonyl group (wherein the alkoxy group may contain from 2 to 6 carbon atoms) substituted in any but the α-position by a hydroxy group may be converted into a compound of general formula I wherein the said hydroxy group is replaced by an acyloxy group, by acylation; and/or a compound of general formula I, wherein W represents a hydroxymethyl group may subsequently be converted (via a corresponding halomethyl compound) by reaction with a malonic acid diester, into a corresponding compound of general formula I wherein W represents an ethyl group substituted by two alkoxycarbonyl groups; and/or a compound of general formula I wherein W represents a formyl group may subsequently be converted by condensation and optional subsequent hydrolysis and/or decarboxylation into a corresponding compound of general formula I wherein W represents a vinyl group substituted by a hydroxycarbonyl or alkoxycarbonyl group; and/or a compound of general formula I wherein W represents an ethyl group substituted by two alkoxycarbonyl groups may subsequently be converted by hydrolysis and decarboxylation into a corresponding compound of general formula I wherein W represents an ethyl group substituted by a carboxy group; and/or a compound of general formula I wherein W represents a carboxy group may subsequently be converted via a sulfonic acid hydrazide and subsequent disproportionation into a corresponding compound of general formula I wherein W represent a formyl group; and/or a compound of general formula I wherein R_1 and R_2 together with the nitrogen atom to which they are attached represent an aza-1,4-dioxa-spiro-alkyl group containing 6 to 8 carbon atoms, may subsequently be converted by means of hydrolysis in the presence of an acid

into a corresponding compound of general formula I wherein R_1 and R_2 together with the nitrogen atom to which they are attached represent an unbranched alkyleneimino group containing 4 to 6 carbon atoms wherein a methylene group is replaced by a carbonyl group; and/or a compound of general formula I wherein R_1 and R_2 together with the nitrogen atom to which they are attached represent an unbranched alkyleneimino group containing 4 to 6 carbon atoms, wherein a methylene group is replaced by a carbonyl group, may subsequently be converted by means of reduction into a corresponding hydroxy-alkyleneimino compound of general formula I; and/or a compound of general formula I wherein W represents an aminocarbonyl group may subsequently be converted by means of dehydration into a corresponding compound of general formula I wherein W represent a cyano group.

The dehydratation is preferably carried out with a dehydrating agent such as for example phosphorus pentoxide, sulfuric acid or p-toluene sulfonic acid chloride optionally in a solvent such as methylene chloride or pyridine at temperatures between 0 and 100°C, preferably, at temperatures between 20 and 80°C.

The esterification is conveniently carried out in a solvent, such as, for example, the corresponding alcohol, pyridine, toluene, methylene chloride, tetrahydrofuran or dioxan, in the presence of an acid-activating and/or dehydrating agent such as thionyl chloride, ethyl chloroformate, carbonyl diimidazole, N,N'-dicyclohexylcarbodiimide or the isourea ether thereof, optionally in the presence of a reaction accelerator such as copper chloride or by transesterification, e.g. with a corresponding carbonic acid diester, at temperatures between 0 and 100°C, preferably, however, at temperature between 20°C and the boiling temperature of the corresponding solvent.

The amidation is conveniently carried out in a solvent such as methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxan, benzene, toluene, acetonitrilie or dimethyl formamide, optionally in the presence of an acid activating agent or a dehydratng agent, e.g. in the presence of ethyl chloroformate, thionyl chloride, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexyl carbodiimide, N,N'-dicyclohexyl carbodiimide/N-hydroxy succinimide, N,N'-carbonyldiimidazole, N,N'-thionyliddmidazole, or triphenyl phosphine/carbon tetrachloride, or of an agent activating the amino group, e.g. phosphorus trichloride, and optionally in the presence of an inorganic base such as sodium carbonate or a tertiary organic base such as triethylamine or pyridine, which simultaneously may serve as solvent, at temperatures between −25 and 250°C, preferably, however, at temperatures between −10°C and the boiling temperature of the used solvent. The reaction may also be carried out without a solvent. Moreover the water, which is formed during the reaction, may be removed by means of azeotropic distillation, e.g. by heating with toluene in a water separator funnel, or by addition of a drying agent such as magnesium sulfate or a molecular sieve.

The reduction of the nitro compound is preferably carried out in a solvent such as water, water/ethanol methanol, glacial acetic acid, ethyl acetate or dimethyl formamide appropriately with hydrogen in the presence of a hydrogenation catalyst such as Raney-nickel, platinum or palladium/charcoal, with metals such as iron, tin or zinc in the presence of an acid, with metal salts such as iron(II)sulfate, tin(II)chloride or sodium dithionite, or with hydrazine in the presence of Raney-nickel at temperatures between 0 and 50°C, preferably, however, at room temperatures.

The reaction of the diazonium salt, (e.g. the fluoroborate, the hydrosulfate in sulfuric acid, the hydrochloride or the hydroiodide) is carried out, if necessary, in the presence of copper or a corresponding copper (I) salt such as copper (I) chloride/hydrochloric acid, copper (I) bromide/hydrobromic acid, trisodium copper(1)tetracyanide at pH 7, or an alkali metal xanthogenate, or copper (II) chloride/sulfur dioxide in glacial acetic acid optionally with the addition of magnesium chloride, at slightly elevated temperatures, e.g. at temperatures between 15 and 100°C. The subsequent reaction with hypophosphorous acid is preferably carried out at −5 to 0°C. The diazonium salt is conveniently prepared in a solvent such as, for example water/hydrochloric acid, methanol/hydrochloric acid, ethanol/hydrochloric acid or dioxan/hydrochloric acid, by means of diazotization of a corresponding amino compound with a nitrite, e.g. sodium nitrite or an ester of nitrous acid, at lower temperatures, e.g. at temperatures between −10 and 5°C.

The acylation is conveniently carried out in a solvent such as methylene chloride, ether tetrahydrofuran or in an excess of the used acylating agent e.g. formic acid, acetic acid or propionic acid. or their anhydrides, acid chlorides or esters, optionally in the presence of an inorganic or a tertiary organic base, which simultaneously may serve as solvent, and optionally in the presence of an acid-activating agent or of a dehydrating agent at temperatures between −25 and 150°C, preferably, however, at temperatures between −10°C and the boiling temperature of the reaction mixture.

The N-alkylation is conveniently carried out with a corresponding halide or sulfonic acid ester, (e.g. methyl iodide, dimethyl sulfate, ethyl bromide or p-toluenesulfonic acid ethyl ester), optionally in the presence of a base such as sodium hydride, potassium hydroxide or potassium tert.butylate and preferably in a solvent such as for example, diethyl ether, tetradhydrofuran,

dioxan, ethanol, pyridin r dimethyl formamid , at temperatures between 0 and 75°C; preferably, however, at room temperature. The methylation may, also be carried out with formaldehyde/formic acid (appropriat ly at the boiling temperature of the reaction mixture) and the alkylation may be carried out with a corresponding carbonyl compound in the presence f a hydride such as sodium cyanoborohydride in a solvent such as acetonitrile acetic acid or dimethyl formamide/acetic acid preferably at pH 7 and at temperatures between 0 and 50°C.

The dehalogenation is conveniently carried out in a solvent such as methanol, ethanol, ethyl acetate, glacial acetic acid or dimethyl formamide by means of catalytically activated hydrogen, e.g. with hydrogen in the presence of platinum or palladium/charcoal, at temperatures between 0 and 75°C, preferably, however, at room temperature, and at a hydrogen pressure of 1–5 bar.

The hydrolysis is conveniently carried out either in the presence of an acid such as hydrochloric sulfuric, phosphoric, polyphosphoric or trifluoroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide in a solvent such as for example, water, ethanol, water/ethanol, water/isopropanol or water/dioxan at elevated temperatures, e.g. at the boiling temperature of the reaction mixture. The hydrolysis can however, be also carried out with a nitrite, e.g. sodium nitrite, in the presence of an acid such as sulfuric acid, whereby this may conveniently serve simultaneously as solvent, at temperatures between 0 and 50°C. The subsequent alcoholysis is conveniently carried out in the presence of a hydrogen halide, e.g. hydrogen chloride, at tmeperatures between 20°C and the boiling temperauere of the used alcohol.

The reduction is preferably carried out with a metal hydride, e.g. with a complex metal hydride such as lithium aluminium hydride, in a solvent such as, for example, diethyl ether, tetrahydrofuran or dioxan at temperatures between 0 and 100°C, preferably however, at temperature between 20 and 60°C.

The O-alkylation is conveniently carried out with a corresponding halide, sulfonic acid ester or diazoalkane, e.g. with methyl iodide, dimethyl sulfate, ethyl bromide, p-toluene sulfonic acid ethyl ester, methanesulfonic acid isopropyl ester or diazomethane optionally in the presence of a base such as sodium hydride, potassium hydroxide or potassium-tert. butylate and preferably in a solvent such as diethyl ether, tetrahydrofuran, dioxan, methanol, ethanol, pyridine or dimethyl formamide at temperatures between 0 and 75°C, preferably, however, at room temperature.

The conversion of a hydroxymethyl group into a halomethyl group is carried out with a halogenating agent such as for example, thionyl chloride, phosphorus trichloride, phosphorus tribromide or phosphorus pentachloride in a solvent such as methylene chloride, carbon tetrachloride, benzene or nitrobenzene and subsequent reaction with a malonic acid ester, e.g. with an alkali salt of the malonic acid diethyl ester, at temperatures between 0 and 100°C, preferably, however, at temperatures between 20 and 50°C.

The condensation of a formyl compound is conveniently carried out in a solvent such as pyridine or tertahydrofuran with malonic acid, with a malonic acid ester, with a dialkylphosphonoacetic acid ester or an alkoxycarbonylmethylene-triphenyl-phosphone, optionally in the presence of a base as a condensation agent, e.g. in the presence of piperidine, potassium-tert.butylate or sodium hydride, at temperatures between 0 and 100°C. By subsequent acidification, (e.g. with hydrochloric or sulfuric acid) or by subsequent alkaline hydrolysis, the desired acid is obtained.

The hydrolysis is decarboxylation is conveniently carried out in the presence of an acid such as hydrochloric, sulfuric, phosphoric, polyphosphoric or trifluoroacetic acid in a solvent such as for example, water, ethanol, water/ethanol, water/isopropanol or water/dioxan at elevated temperatures, e.g. at the boiling temperature of the reaction mixture.

The disproportonation of a sulfonic acid hydrazide, which is obtained by reacting the corresponding hydrazine with the corresponding reactive carboxylic acid derivative, is carried out in the presence of a base such as sodium carbonate in a solvent such as ethylene glycol at temperatures between 100 and 200°C, preferably, however, at 160–170°C.

The compounds of general formula I obtained by the above processes may if desired be converted into their addition salts, especially into their physiologically compatible salts with inorganic or organic acids or bases by conventional methods such as by reacting the compounds as bases with a solution of the corresponding acids in a suitable solvent, or by reacting the compounds as acids with a solution of the corresponding bases in a suitable solvent. Suitable acids include, for example, hydrochloric acid, hydrochloric acid, hydrobromic acid sulfuric acid, phosphoric acid, lactic acid, citric acid, tartaric acid, succinic acid, maleic acid and fumaric acid. Suitable bases includ , for example, sodium or potassium hydroxid and cycl hexylamin .

Th compounds of general formula II t XIV used as starting materials are known from the literature r may b prepared according to known processes.

Thus, for example, a compound of general formula II wherein A represents a bond can be btained by reduction f the corresponding nitro compound, f r example by means of catalytically activated or nascent hydrogen or by means f sodium dithionite or by reaction of the corresp nding compound by a Hofmann, Curtius, Loss n, or Schmidt reaction.

For example a compound of general formula II, wherein, A represents a vinylidene group or the taut meric ketimine can be btained by reaction of the corresponding nitrile with the corresp nding Grignard r lithium compound and subsequent hydrolysis or by reaction of the corresponding ketone with the corresponding amin in th presence of titanium tetrachlorid . For further reaction with a compound f gen ral formula III r its reactive d rivatices, especially acid chlorides, an organometallic complex can be used.

For example a compound of general formula II, wherein A does not represent a bond or a vinylidene group, can be obtained by reduction of the corresponding nitrile with lithium aluminium hydride, by reaction of the corresponding nitrile with the corresponding Grignard or Lithium compound and optionally with subsequent lithium aluminium hydride reduction or subsequent hydrolysis to the ketimine, which subsequently is reduced with catalytically activated hydrogen, with a complex metal hydride or with nascent hydrogen, by hydrolysis or by hydrazinolysis of the corresponding phthalimido compound, by reaction of the corresponding ketone with ammonium formate and subsequent hydrolysis or with a ammonium salt in the presence of sodium cyanoborohydride, by reduction of the corresponding oxime with lithium aluminium hydride, with catalytically activated or nascent hydrogen, by reduction of the corresponding N-benzyl or N-1-phenylethyl Schiff's base, e.g. with a complex metal hydride in ether or tetrahydrofuran at temperatures between −78° and the boiling temperature of the used solvent and subsequent cleavage of the benzyl or 1-phenylethyl group by means of catalytic hydrogenation by Ritter reaction of a corresponding alcohol and potassium cyanide in sulfuric acid, or by a Hofmann, Curtius, Lossen or Schmidt reaction. An amine of general formula II thus obtained with a chiral center can be resolved, e.g. by fractional crystallization of the diastereoisomeric salts using optionally active acids and subsequent decomposition of the salts or by the formation of diastereoisomeric compounds, their separation and subsequent resolution into enantiomers. Furthermore, an optionally active amine of general formula II can also be prepared by enantioselective reduction of the corresponding ketimine by means of complex boron or aluminium hydrides, in which some of the hydride hydrogen atoms are replaced by optically active alcoholate radicals, or by means of hydrogen in the presence of a suitable chiral hydrogenation catalyst, or in an analogous manner starting from an N-benzyl or optionally optically active N-1-phenethyl Schiff's base and optionally subsequent cleavage of the benzyl or 1-phenethyl radical.

A compound of general formula II wherein R_4 represents a lower alkyl radical may be obtained by reduction of the corresponding N-acyl compound, e.g. by means of lithium aluminium hydride.

The compounds of general formulae IV, V, and VII to X used as starting materials may each be obtained by reaction of an amine with a carboxylic acid or one of its reactive derivatives and optional subsequent hydrolysis. A compound of general formula VIII can be obtained by Friedel-Crafts acetylation of the corresponding acetyl-unsubstituted compound.

A compound of general formula XII used as a starting material can be obtained preferably by acrylation of the corresponding ketimine or tautomeric forms with the corresponding carboxylic acid or one of its reactive derivatives.

A compound of general formula XIII used as a starting material can be obtained by reduction of the corresponding carbonyl compound with the corresponding Grignard or lithium reagent.

The compounds of general formula I posses valuable pharmacological properties, and in general show beneficial effects on intermediary metabolism, and especially, however, a blood-sugar lowering activity.

For example the following compounds have been tested with regard to their biological properties:

A = 4-[2-Pyrrolidino-benzyl)-aminocarbonylmethyl]benzoic acid,
B = 4-[(1-(2-Pyrrolidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid,
C = 4-[(1-(5-Chloro-2-pyrrolidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid,
D = 4-[(2-Piperidino-benzyl)-aminocarbonylmethyl]benzoic acid,
E = 4-[(1-(2-Piperidino-phenyl)-ethenyl)-aminocarbonylmethyl]benzoic acid,
F = 4-[(1-(6-Chloro-2-piperidino-phenyl)-ethenyl)-aminocarbonylmethyl]benzoic acid,
G = 4-[(1-(6-Methyl-2-piperidino-phenyl)-ethenyl)-aminocarbonylmethyl]benzoic acid,
H = 4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl)benzoic acid,
I = Ethyl 4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoate,
K = (+)Ethyl 4-[(1-(1-Pip ridino-ph nyl)-ethyl)-aminocarbonylm thyl]benzoate
L = 4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarb nylmethyl]benzoic acid-(2,2-dimethyl-di xolane-4-yl)-methyl ester,
M = 4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]tolu ne,
N = 4-[(1-(2-Piperidino-ph nyl)-ethyl)-aminocarbonylmethyl]benzyl alcoh l,
O = 4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarb nylmethyl]benzaldehyde,
P = 4-[(1-(2-Pip ridino-ph nyl)-ethyl)-aminocarbonylmethyl]ph nyl acetic acid,
Q = 4-[(1-(4-Chloro-2-piperidino-phenyl)-ethyl)-aminocarbonylm thyl]benzoic acid,

R = 4-[(1-(5-Chloro-2-piperidino-phenyl)-ethyl)-amin carbonyl-methyl]b nzoic acid,
S = Ethyl 4-[(1-(6-Chloro-2-pip ridino-phenyl)-ethyl)-aminocarbonylmethyl]benzoate,
T = 4-[(1-(5-Fluoro-2-piperidino-phenyl)-ethyl)-aminocarbonyl-methyl]benzoic acid,
U = 4-[(1-(4-Methyl-2-piperidino-phenyl)-ethyl)-aminocarbonyl-methyl]benzoic acid,
V = 4-[(1-(5-M thyl-2-pip ridino-ph nyl)-ethyl)-amin carb nyl-methyl]benzoic acid,
W = 4-[(2-(2-Piperidino-phenyl)-2-propyl)-aminocarbonylmethyl]benzoic acid,
X = 4-[(1-(2-Piperidino-phenyl)-2-methyl-propyl)-aminocarbonyl-methyl]benzoic acid,
Y = 4-[(2-Piperidino-benzhydryl)-aminocarbonylmethyl]benzoic acid,
Z = 4-[(1-(2-(1,2,3,6-Tetrahydro-pyridino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid,
AA = 4-[(1-(2-(3-Methyl-piperidino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid,
AB = 4-[(1-(2-Hexahydroazepino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid,
AC = 4-[(1-(2-Octahydroisoindolo-phenyl)-ethyl)-aminocarbonyl-methyl]benzoic acid,
AD = Ethyl 4-[(α-Methoxycarbonyl-2-piperidino-benzyl)-aminocarbonylmethyl]benzoate and
AE = (+) 4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid.

1. *Blood-sugar lowering activity:*

The blood-sugar lowering activity of the test compounds was determined in home-bred female rats with a weight of 180–220 g. 24 hours before starting the test the animals were starved. Before the test the compounds were suspended in 1.5% methyl cellulose and administered to the animals by means of an oesophageal tube.

Blood was taken before administering the test compounds as well as at 1, 2, 3 and 4 hours after administration from the retroorbital plexus vein. 50 µg of each sample were deproteinized with 0.5 ml of 0.33 N perchloric acid and centrifuged. The glucose content in the supernatant was determined according to the Hexokinase method by means of an analysis photometer. The statistical evaluation was performed with the t-test according to Student with $p = 0.05$.

Th following tabl contains the obtain d values in percent compared with th controls:

Table 1:

Test compound	25 mg/kg				10 mg/kg				5 mg/kg			
	1 hours	2	3	4	1 hours	2	3	4	1 hours	2	3	4
A					−36	−23	−14	n.s.	−22	n.s.	−10	n.s.
B					−42	−35	−31	−13	−38	−18	n.s.	n.s.
C	−40	−30	−26	−22	−26	−17	n.s.	n.s.				
D					−38	−36	−25	−14	−27	−16	−11	−13
E					−42	−39	−34	−32	−45	−41	−36	−21
F	−45	−42	−38	−32	−44	−39	−32	−24	−47	−33	−26	n.s.
G									−31	−15	n.s.	n.s.
H	−40	−43	−45	−38	−45	−38	−35	−30	−45	−45	−36	−32
I					−24	−27	−17	−13	−22	−22	n.s.	n.s.
K									−47	−42	−31	−22
L					−39	−37	−32	−24	−43	−34	−29	−19
M	−45	−44	−38	−32								
N					−40	−40	−30	−31	−35	−29	n.s.	n.s.
O	−46	−47	−37	−36	−46	−41	−39	−35	−43	−35	−26	−23
P					−41	−26	−19	n.s.	−27	−18	n.s.	n.s.
Q					−35	−39	−33	−30				
R	−36	−36	−34	−28	−36	−34	−26	−20	−17	−18	−11	n.s.
S	−44	−46	−39	−37								
T					−49	−47	−46	−46	−43	−36	−29	−29
U					−37	−18	n.s.	n.s.	−42	−15	n.s.	n.s.
V	−28	−23	−25	−20								
W					−32	−34	−27	−20	−19	−24	−16	n.s.
X	−46	−45	−43	−36	−43	−41	−36	−28	−36	−40	−32	−32
Y	−44*	−44*	−41*	−42*					−44	−38	−41	−37
Z									−45	−39	−35	−31
AA	−46	−38	−44	−46	−42	−32	−26	−35	−48	−36	−33	−20
AB	−45	−46	−39	−34	−41	−35	−24	−17	−29	−18	n.s.	n.s.
AC	−41	−44	−32	−26								
AD					−40	−32	−31	−17				
AE**									−41	−34	−20	n.s.

* = dose: 20 mg/kg
** = dose: 1 mg/kg
n.s. = statistically not significant

2. *Acute toxicity:*

The acute toxicity was determined in home-bred female and male mice with a body weight of 20–26 g after oral administration (suspension in 1% methyl cellulose) of a single dose.

Observation time: 14 days

The following table contains the values obtained:

Test compound	orientating toxicity
H	>2 000 mg/kg p.o. (1 out of 10 animals died)
R	>2 000 mg/kg p.o. (0 out of 10 animals died)
Y	>2 000 mg/kg p. . (0 out f 6 animals died)

The compounds of gen ral formula I ar suitable for the treatment of diabetes mellitus due to their b nefical effects on int rmediary m tabolism and th ir blood-sugar lowering activity.

According to a yet further feature of the present invention ther ar provided pharmaceutical compositions comprising as active ingr dient at least one compound of general formula I as hereinbefore d fined or a physiologically compatible salt th reof, in association with one or more

pharmaceutical carriers or xcipients.

F r pharmaceutical administration, the compounds f gen ral formula I or their physi logically compatibl salts may be incorporated into conv nti nal preparations in either solid or liquid form, optionally in combinati n with oth r active ingredients. The c mpositions may, for example, be presented in a form suitable for oral or parenteral administration. Preferred forms include, for example, tablets, coated tablets, capsules, powders or suspensions.

The active ingredient may be incorporated in excipients customarily employed in pharmaceutical compositions such as for example, corn starch, lactose, magnesium stearate, aqueous or non-aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, polyvinyl pyrrolidone, potato starch, various wetting, dispersing or emulsifying agents and/or preservatives.

Advantageously the compositions may be formulated as dosage units, each dosage unit being adapted to supply a fixed dose of active ingredient. Suitable single dosage units for adults contain from 1 to 50 mg, preferably 2.5 to 20 mg of active ingredient according to the invention. Such dosage units may, for example, be administered 1 or 2 times daily. The total daily dosage may, however, be varied according to the compound used, the subject treated and the complaint concerned.

According to a yet further feature of the present invention there is provided a method of treating a patient suffering from, or susceptible to disorders of intermediary metabolism and/or blood sugar which comprises administering to the said patient an effective amount of a compound of formula I, as hereinbefore defined, or a physiologicaly compatible salt thereof.

The following non-limiting examples serve to illustrate the present invention:

Example 1

4-[(1-(5-Chloro-2-dimethylamino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid methyl ester

1.67 g (0.0103 mol) of carbonyl diimidazole were added with stirring at 20°C to a solution of 2.00 g (0.0103 mol) of 4-methoxycarbonyl-phenyl acetic acid in 13.5 ml of absolute tetrahydrofuran. Subsequently the mixture was heated to reflux temperature for 45 minutes excluding moisture. After cooling to room temperature 2.05 g (0.0103 mol) of 1-(5-chloro-2-dimethylamino-phenyl)-ethylamine in 7 ml of absolute tetrahydrofuran were added and the reaction mixture was stirred over night at 20°C. After evaporating *in vacuo* the evaporation residue was purified by column chromatography on silica gel (toluene/acetone = 10/1).

Yield: 2.6 g (66.7% of theory),
M.p.: 153–155°C (from ether).

Calc.:	C 64.08	H 6.18	Cl 9.46	N 7.47
Found:	64.30	6.04	9.70	7.39

Analogously to Example 1 the following compounds were prepared:

4-[(1-(5-Chloro-2-dipropylamino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid methyl ester

Yield: 42% of theory,
M.p: 135– 137°C (from ether/petroleum ether)

Calcd.:	C 66.83	H 7.25	Cl 8.23	N 6.50
Found:	66.95	7.35	8.35	6.05

4-[(1-(5-Chloro-2-dibutylamino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid methyl ester
Yield: 64.8% of theory,
M.p.: 110–112°C.

Calc.:	68.03	H 7.69	Cl 7.72	N 6.10
Found:	67.86	7.61	7.73	6.17

4-[(1-(5-Chloro-2-N-cyclohexyl-N-methylamino-phenyl)ethyl)-aminocarbonylmethyl]benzoic acid methyl ester
Yield: 63.9% of theory,
M.p.: 152–153°C (ether).

Calc.:	C 67.78	H 7.05	Cl 8.00	N 6.32
F und:	67.70	6.92	8.24	6.46

4-[(5-Chloro-2-pyrrolidino-benzyl)-aminocarbonylmethyl]benzoic acid methyl ester
Yield: 68.1% f theory,
M.p.: 139–141°C (methan l)

Calc.:	C 65.19	H 5.99	Cl 9.17	N 7.24
Found:	65.46	5.91	9.26	7.41

4-[(1-(5-Chloro-2-pyrrolidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid methyl ester
Yield: 58.3% of theory,
M.p.: 133–135°C (methanol)

Calc.:	C 65.91	H 6.29	Cl 8.84	N 6.99
Found:	66.24	6.19	8.75	7.13

4-[(5-Chloro-2-piperidino-benzyl)-aminocarbonylmethyl]benzoic acid methyl ester
Yield: 75.1% of theory,
M.p.: 123–125°C (ether)

Calc.:	C 65.91	H 6.29	Cl 8.84	N 6.99
Found:	66.05	6.13	8.86	7.21

4-[(1-(5-Chloro-2-piperidino-benzyl)-aminocarbonyl)-ethyl]benzoic acid methyl ester
Yield: 70.4% of theory,
M.p.: 142–144°C (ether).

Calc.:	C 66.57	H 6.56	Cl 8.55	N 6.75
Found:	66.50	6.49	8.44	6.86

4-[(1-(5-Chloro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid methyl ester
Yield: 69.5% of theory,
M.p.: 147–149°C (ether).

Calc.:	C 66.57	H 6.56	Cl 8.55	N 6.75
Found:	66.33	6.54	8.67	6.85

4-[(1-(5-Chloro-2-(3-methyl-piperidino)-phenyl)ethyl)-aminocarbonylmethyl]benzoic acid methyl ester
Yield: 54.3% of theory,
M.p.: 160–162°C (methanol).

Calc.:	C 67.20	N 6.81	Cl 8.27	N 6.53
Found:	67.27	6.81	8.13	6.45

4-[(1-(5-Chloro-2-(3,5-cis-dimethyl-piperidino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid methyl ester
Yield: 44% of theory,
M.p.: 190–193°C (methanol)

Calc.:	C 67.78	H 7.05	Cl 8.00	N 6.32
Found:	67.50	7.05	8.25	6.48

4-[(1-(5-Chloro-2-piperidino-phenyl)-propyl)-aminocarbonylmethyl]benzoic acid methyl ester
Yield: 65.9% of theory,
M.p.: 142–144°C (ether).

Calc.:	C 67.20	H 6.81	Cl 8.26	N 6.53
Found:	67.45	6.63	8.38	6.63

4-[(1-(5-Chloro-2-piperidino-phenyl)-2-methyl-propyl)-aminocarbonylmethyl]benzoic acid methyl ester
Yield: 61.4% of theory,
M.p.: 156–158°C (ether).

Calc.:	C 67.78	H 7.05	Cl 8.00	N 6.32
Found:	67.80	7.17	7.89	6.28

4-[(1-(5-Chloro-2-morpholino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid methyl ester
Yield: 69.8% of theory,
M.p.: 156–158°C (ether).

	C	H	Cl	N
Calc.:	63.38	6.04	8.50	6.72
Found:	63.24	6.12	8.70	6.85

4-[(1-(5-Chloro-2-thiomorpholino-phenyl)-ethyl)-aminocarbonylmethyl/benzoic acid methyl ester
Yield: 68.2% of theory,
M.p.: 167–169°C (ether).

	C	H	Cl	N	S
Calc.:	61.03	5.82	8.19	6.47	7.41
Found:	60.83	5.77	8.33	6.49	7.39

4-[(1-(5-Chloro-2-(hexahydro-1H-azepino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid methyl ester
Yield: 41.7% of theory,
M.p.: 146–147°C (methylene chloride/petroleum ether).

	C	H	Cl	N
Calc.:	67.19	6.81	8.27	6.53
Found:	66.90	6.66	8.30	6.39

4-[(1-(5-Chloro-2-octahydroazocino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid methyl ester
Yield: 30% of theory,
M.p.: 154–156°C

Calc.: mol peak m/e = 442/444 (1 chlorine)
Found: m/e = 442/444 (1 chlorine)

4-[(1-(5-Chloro-2-(octahydro-1H-azonino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid methyl ester
Yield: 38% of theory,
M.p.: 184–185°C (chloroform/toluene)

	C	H	N
Calc.:	68.32	7.28	6.13
Found:	68.10	7.30	6.28

4-[(2-(5-Chloro-2-piperidino-phenyl)-2-propyl)-aminocarbonylmethyl]benzoic acid methyl ester
Yield: 84.4% of theory,
M.p.: 162–164°C

Calc.: mol peak m/e = 428/430 (1 chlorine)
Found: m/e = 428/430 (1 chlorine)

4-[(1-(5-Nitro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid methyl ester
Yield: 68.3% of theory,
M.p.: 178–180°C (toluene)

	C	H	N
Calc.:	64.93	6.40	9.88
Found:	65.05	6.43	9.87

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid methyl ester
Yield: 59.1% of theory,
M.p.: 145–147°C

	C	H	N
Calc.:	72.61	7.42	7.36
Found:	72.35	7.39	7.40

4-[(5-Methyl-2-piperidino-benzyl)-aminocarbonylmethyl]benzoic acid methyl ester
Yield: 32.9% of theory,
M.p.: 124–126°C (petroleum ether/acetone)

Calc.: mol peak m/e = 380
Found: m/ = 380

N-(4-Nitro-phenacetyl)-N-[1-(2-piperidino-phenyl)-ethyl]amine
Yield: 62.4% of theory,
M.p.: 165–167°C (ether)

Calc.:	C 68.64	H 6.86	N 11.44	
F und:	68.73	6.88	11.63	

N-(4-Acetyl-phenacetyl)-N-[1-(2-piperidino-phenyl)-ethyl]amine
Yield: 32.4% of theory,
M.p.: 162–164°C (ether)

Calc.:	C 75.79	H 7.74	N 7.69
Found:	75.51	7.86	7.38

N-(4-Acetyl-phenacetyl)-N-[1-(5-chloro-2-piperidino)phenyl)-ethyl]amine
Yield: 50.3% of theory,
M.p.: 162–163°C (ether)

Calc.:	C 69.24	H 6.82	N 7.02
Found:	66.88	6.63	6.70

2-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid methyl ester
Yield: 82% of theory,
M.p.: 107–108°C

Calc.:	C 72.60	H 7.42	N 7.36
Found:	72.79	7.38	7.53

3-[1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 47% of theory,
M.p.: 155°C

Calc.:	C 73.07	H 7.67	N 7.10
Found:	73.30	7.58	7.17

3-Chloro-4-[(1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 63% of theory,
M.p.: 123–124°C

Calc.:	C 67.20	H 6.81	Cl 8.27	N 6.53
Found:	67.28	6.84	8.36	6.50

4-[(1-(2-(1,2,3,4-Tetrahydro-isoquinoline-2-yl)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 43% of theory,
M.p.; 142–144°C

Calc.:	C 75.99	H 6.83	N 6.33
Found:	75.64	6.75	6.35

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]toluene
Yield: 59% of theory,
M.p.: 136–138°C

Calc.:	C 78.53	H 8.39	N 8.33
Found:	78.58	8.16	8.26

4-[(5-Chloro-2-piperidino-anilino)-carbonylmethyl]benzoic acid methyl ester
Yield: 40.3% of theory,
M.p.: 156–158°C (methanol/toluene)

Calc.:	C 65.19	H 5.99	Cl 9.16
Found:	65.20	6.15	9.40

4-[2-(2-Piperidino-anilino-carbonyl)-ethyl]benzoic acid-methyl ester
Yield: 26.9% f theory,
M.p.: 71–73°C (petroleum ether)

Calc.:	C 72.10	H 7.15	N 7.65	
Found:	72.00	7.09	7.94	

4-[(1-(2-(1,2,3,6-Tetrahydro-pyridino)-phenyl)-ethyl)-amino-carbonylmethyl]benzoic acid ethyl ester
Yield: 63.4% of theory,
M.p.: 125–127°C (ether)

Calc.:	C 73.44	H 7.19	N 7.14	
Found:	73.38	7.13	7.13	

4-[(2-(5-Chloro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 68% of theory,
M.p.: 95–97°C (ethanol)

Calc.:	C 67.20	H 6.81	Cl 8.27	N 6.53
Found:	67.75	6.76	8.22	6.24

4-[(1-(5-Fluoro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 47.3% of theory,
M.p.: 138–140°C (ether)

Calc.:	C 69.88	H 7.99	N 6.79
Found:	70.10	7.10	6.87

4-[(1-(5-Nitro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 56.5% of theory,
M.p.: 144–147°C (ethanol)

Calc.:	C 65.59	H 6.65	N 9.56
Found:	65.78	6.56	9.73

4-[(2-(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonyl)-ethyl]benzoic acid methyl ester
Yield: 90% of theory,
M.p.: 129–131°C

Calc.:	C 73.06	H 7.67	N 7.10
Found:	72.61	7.77	7.52

4-[(2-Hydroxy-1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 44.4% of theory,
M.p.: 132–135°C (petroleum ether/acetone)

Calc.:	C 70.22	H 7.37	N 6.82	m/e = 410
Found:	70.02	7.25	6.77	m/e = 410

4-[(1-(5-Hydroxy-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 64.2% of theory,
M.p.: 150–151°C (ether)

Calc.:	C 70.22	H 7.37	N 6.82	m/e = 410
Found:	70.37	7.17	6.81	m/e = 410

4-[(α-Methoxycarbonyl-2-piperidino-benzyl)aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 59% of theory,
M.p.: 110–112°C (petroleum ether/acetone)

Calc.:	C 68.47	H 6.90	N 6.39	m/e = 438
Found:	68.57	6.64	6.46	m/ = 438

4-[(1-(5-Chloro-2-(2-methyl-piperidino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 71.3% of theory,
M.p.: <20°C

Calc.: m/ = 442/444 (1 chlorine)
Found: m/e = 442/444 (1 chlorin)

4-[(1-(2-Hexahydroazepino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 68% of theory,
M.p.: 145–148°C (toluene)

Calc.:	C 73.50	H 7.90	N 6.86
Found:	73.35	8.04	6.89

4-[(1-(2-[1,4-Dioxa-8-azaspiro[4,5]decyl-(8)]phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 64.3% of theory,
M.p.: 143–145°C (petroleum ether/acetone)

Calc.:	C 69.01	H 7.13	N 6.19
Found:	69.30	7.38	6.21

4-[(1-(2-(2-Methyl-pyrrolidino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 72% of theory,
M.p.: 94–97°C

Calc.:	C 73.07	H 7.66	N 7.10
Found:	72.25	7.67	7.11

4-[(1-(3-Methyl-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 39,5% of theory), m.p. 178–179°C
Calc.: m/e = 408
Found: m/e = 408

4-[(1-(3-Chloro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 52,6% of theory,
Calc.: m/e = 428/430 (1 chlorine)
Found: m/e = 428/430 (1 chlorine)

Example 2
(+) 4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
231.4 mg (1.43 m mol) of carbonyl diimidazole were added to a solution of 290.9 mg (1.40 m mol) of 4-ethoxycarbonylphenyl acetic acid in 6 ml of tetrahydrofuran. Subsequently the mixture was heated to reflux temperature for 1.5 hours excluding moisture. After cooling to room temperature 0.385 ml (≙ 2.78 m mol) of triethylamine (dried over potassium hydroxide) and 360 mg (1.30 m mol) of (+) 1-(2-piperidino-phenyl)-ethylamine dihydrochloride [m.p. 242°C (decomp.); $[\alpha]_D^{20}$ = + 14.8° (c = 1; methanol)] together with 2 ml of tetrahydrofuran were added and the mixture was stirred for 4 hours at 50°C in an oil bath. After evaporating *in vacuo* the evaporation residue was distributed between chloroform and water. The chloroform extract was dried over sodium sulfate, filtered through a G3-glas frit and evaporated *in vacuo* to dryness. The obtained residue was purified by column chromatography on silica gel (chloroform/methanol = 6:1).

Yield: 229 mg (44.7% of theory),
M.p.: 89–90°C (ether)
$[\alpha]_D^{20}$ = 8.2°C (c = 1; methanol)

Calc.:	C 73.07	H 7.66	N 7.10	m/e = 394
Found:	73.20	7.68	7.14	m/e = 394

Anal gously t Exampl 2 was prepared:

(−) 4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
fr m (−) 1-(2-piperidino-ph nyl)-ethylamino dihydrochloride [m.p.: 239–242°C (decomp.); $[\alpha]_D^{20}$: −19.6° (c = 1; methan l)].
Yi ld: 41.1% of theory,
M.p.: 77–79°C (ether/cyclohexane)
$[\alpha]_D^{20}$ = −6.2° (c = 1; methanol)

Calc.:	C 73.07	H 7.66	N 7.10	m/e = 394
Found:	72.67	7.75	6.82	m/ = 394

Example 3

4-[(1-(4-Chloro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester

2.3 ml (0.023 mol) of carbon tetrachloride were added to a solution of 5.5 g (0.023 mol) of 1-(4-chloro-2-piperidinophenyl)-ethylamine, 4.8 g (0.023 mol) of 4-ethoxycarbonylphenyl acetic acid, 7.3 g (0.028 mol) of triphenyl phosphine and 3.2 ml (0.023 mol) of triethylamine in 50 ml of acetonitrile and the mixture was stirred for 24 hours at room temperature. After evaporating *in vacuo* the evaporation residue was distributed between 100 ml of water and ethyl acetate. The combined organic extracts, which were dried over sodium sulfate, were filtered, evaporated *in vacuo* and the evaporation residue was purified by column chromatography on silica gel (toluene/ethyl acetate = 4:1).

Yield: 6.1 g (62% of theory),
M.p.: 126–128°C

Calc.:	C 76.20	H 6.81	Cl 8.27	N 6.53
Found:	67.43	6.97	8.16	6.40

Analogously to Example 3 the following compounds were prepared:

4-[(1-(4-Methyl-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 48.2% of theory,
M.p.: 120–122°C

Calc.:	C 73.50	H 7.89	N 6.86
Found:	73.61	7.95	6.73

4-[(1-(2-(4-Methyl-piperidino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 55.8% of theory,
M.p.: 125–128°C (ether)

Calc.:	C 73.50	H 7.90	N 6.86
Found:	73.30	7.99	7.20

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 71% of theory,
M.p.: 147–148°C

Calc.:	C 73.06	H 7.67	N 7.10
Found:	73.54	8.04	6.95

4-[1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]phenyl acetic acid
Prepared from 1-(2-piperidino-phenyl)-ethylamine and p-phenylene diacetic acid.
Yield: 27% of theory,
M.p.: 186–189°C

Calc.:	C 72.60	H 7.42	N 7.36
Found:	72.75	7.65	7.11

4-[(2-Piperidino-benzhydryl)-aminocarbonylmethyl]-benzoic acid ethyl ester
Yield: 87.4% of theory,
M.p.: 160–162°C

Calc.:	C 76.29	H 7.06	N 6.14
Found:	76.44	7.08	6.17

4-[(5-Chloro-2-piperidino-benzhydryl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 78% of theory,
M.p.: 202–204°C

Calc.:	C 70.93	H 6.36	Cl 7.22	N 5.71
Found:	70.85	6.40	7.11	5.45

4-[(1-(4-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 39% of the ry,
M.p.: 118–120°C

	C	H	N
Calc.:	73.07	7.67	7.10
Found:	73.20	7.78	7.11

4-[(1-(2-(4-Methyl-piperazino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 53% of theory,
M.p.: 130–132°C

	C	H	N
Calc.:	70.38	7.63	10.26
Found:	70.41	7.53	10.13

4-[(1-(2-(4-Benzyl-piperazino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 75% of theory
M.p.: 135–136°C

	C	H	N
Calc.:	74.20	7.26	8.66
Found:	74.45	7.34	8.54

4-[(1-(2-(4-p-chlorophenyl-piperazino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 48.5% of theory,
M.p.: 178–180°C

	C	H	N	Cl
Calc.:	68.83	6.37	8.30	7.01
Found:	68.71	6.22	8.41	6.82

4-[(α-Cyclohexyl-2-piperidino-benzyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 75% of theory,
M.p.: 135°C

	C	H	N
Calc.:	75.29	8.28	6.06
Found:	75.11	8,13	5,99

N-(4-Chloro-phenacetyl)-N-[1-(2-piperidino-phenyl)-ethyl]amine
Yield: 79% of theory,
M.p.: 150–152°C

	C	H	Cl	N
Calc.:	70.67	7.06	9.93	7.85
Found:	70.94	7.84	10.09	7.90

4-[(2-Pyrrolidino-benzhydryl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 57% of theory,
M.p.: 163–165°C

	C	H	N
Calc.:	75.99	6.83	6.33
Found:	75.45	6.52	6.10

4-[(2-Hexamethyleneimino-benzhydryl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 68% of theory,
M.p.: 151–154°C

	C	H	N
Calc.:	76.56	7.28	5.95
Found:	76.43	7.19	6.01

Example 4
4-[(1-(2-PPiperidino-phenyl)-ethyl)-aminocarbonylmethyl]-benzoic acid ethyl ester
11.2 g (0.0539 mol) f 4-ethoxycarbonyl-phenylacetic acid, 17 g (0.0647 mol) of triphenyl phosphine, 22.6 ml (0.162 mol) of triethylamine and 5.2 ml (0.0539 mol) of carbon tetrachl rid were successiv ly added with stirring to a solution f 10.9 g (0.0539 mol) of freshly prepared (2-piperidinophenyl)-methyl-ketimin in 100 ml f acetonitrile. The solution, which was clear after a short time, was stirred for 20 hours at 20°C. The resultant precipitate (triethylamine hydrochloride) was filt r d off and the filtrate was evaporat d *in vacuo*. The

evaporation residue was purified by column chromatography on silica gel (toluene/acetone = 10:1).

M.p.: 112–115°C (ether)

	C	H	N
Calc.:	73.44	7.19	7.14
Found:	73.28	7.32	6.96

Analogously to Example 4 the following compounds were prepared:

4-[(α-Cyclohexylidene-2-piperidino-benzyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 24% of theory,
M.p.: 131–133°C

	C	H	N
Calc.:	75.62	7.88	6.08
Found:	75.59	7.47	6.01

4-[(1-(2-Piperidino-phenyl)-propenyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 65,0% of theory (E- and Z-isomeric mixture)
M.p.: of the polar isomer: 82–84°C

	C	H	N
Calc.:	73.85	7.44	6,89
Found:	73.73	7.57	7.01

Example 5

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester

A solution of 60.6 g (0.267 mol) of 4-ethoxycarbonyl-phenacetyl chloride in 120 ml of methylene chloride was dropped with slight ice cooling to a stirred solution of 49.6 g (0.243 mol) of 1-(2-piperidinophenyl)-ethylamine [b.p. 0.6: 100–107°C; m.p. of the dihydrochloride: 234–237°C (decomp.)] and 37.3 ml (0.267 mol) of triethylamine in 245 ml of methylene chloride at an internal temperature of 20–30°C. After stirring for 2 hours at room temperature, the resultant precipitate was filtered off, washed once with methylene chloride, and the combined methylene chloride phases were extracted successively twice with water, once with 10% aqueous ammonia, twice with water, once with 100 ml of 3% hydrochloric acid and twice with water. The methylene chloride phase was dried over sodium sulfate and evaporated *in vacuo*. The evaporation residue was crystallized from ether.
Yield: 88.8 g (92.7% of theory),
M.p.: 148–150°C

Analogously to Example 5 the following compounds were prepared:

4-[(5-Methyl-2-piperidino-benzyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 22.5% of theory,
M.p.: 116.5–117°C (ethanol/petroleum ether)

	C	H	N
Calc.:	73.07	7.66	7.10
Found:	73.48	7.62	7.15

4-[(1-(5-Methyl-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 20.2% of theory,
M.p.: 132–132.5°C (ethanol)

	C	H	N
Calc.:	73.50	7.90	6.86
Found:	73.49	7.74	6.94

4-[(1-(5-Methoxy-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 35.8% of theory,
M.p.: 131–132°C (ethanol)

	C	H	N
Calc.:	70.73	7.60	6.60
Found:	70.98	7.59	6.38

4-[(1-(2-Piperidino-phenyl)-ethyl)-N-methylamino-carbonylmethyl]benzoic acid ethyl ester
Yield: 65.2% f theory,
M.p.: <20°C

Calc.:	C 73.50	H 7.90	N 6.86	
Found:	72.99	7.60	6.87	

4-[(1-(2-Decahydro-isoquinoline-2-yl)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 44% of theory,
M.p.: 159°C

Calc.:	C 74.96	H 8.08	N 6.24
Found:	75.09	8.01	6.01

4-[(1-(2-(1,2,3,4,5,6,7,8-Octahydro-isoquinoline-2-yl)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 35% of theory,
M.p.: 115–117°C

Calc.:	C 75.30	H 7.67	N 6.27	
Found:	75.18	7.37	5.89	

4-[(1-(2-Octahydro-isoindole-2-yl)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 36% of theory,
M.p.: 141°C

Calc.:	C 74.62	H 7.88	N 6.44
Found:	74.70	7.97	6.42

4-[(1-(3-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 24% of theory,
M.p.: 164°C

Calc.:	C 73.07	H 7.66	N 7.10	
Found:	72.80	7.48	7.13	

4-[(1-(6-Chloro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 17% of theory,
M.p.: <20°C

Calc.:	C 67.20	H 6.81	Cl 8.26	N 6.53	m/e = 428/30
Found:	67.96	6.56	8.80	6.67	m/e = 428/30

4-[(1-(6-Methyl-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 3.5% of theory,
M.p.: <20°C

Calc.:	C 73.49	H 7.89	N 6.85	m/e = 408
Found:	73.80	7.61	7.01	m/e = 408

4-[(1-(2-(3-Aza-bicyclo[3.2.2]nonane-3-yl)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 0.5% of theory,
M.p.: <20°C

Calc.:	m/e = 434
Found:	m/e = 434

N-[1-(5-Chloro-2-piperidino-phenyl)-ethyl]-N-phenacetylamine
Yield: 53.5% of theory,
M.p.: 134–136°C (thanol)

Calc.:	C 70.67	H 7.06	Cl 9.94	N 7.85
Found:	70.40	7.32	9.77	7.68

Example 6

4-[(1-(2-Piperidino-phenyl)-ethenyl)-aminocarbonylmethyl]benzoic acid ethyl ester

A solution of 2.49 g (0.011 mol) of 4-ethoxycarbonylphenacetyl chloride in 10 ml f methylen chloride was added with ice cooling over 15 minutes to a stirred solution of 2.02 g (0.010 mol) of freshly prepared methyl-(2-piperidinophenyl)-ketimine and 1.53 ml f (0.011 mol) of triethylamine in 10 ml of methylene chloride at an internal temperature of 1 to 6°C. The reaction mixture was stirred for 20 minutes at 20°C and poured into cold sodium hydrogen carbonate solution. After extracting several times the organic extract was washed once with water, dried over sodium sulfate, filtered, and evaporated *in vacuo*. The evaporation residue was purified by column chromatography on silica gel (toluene/acetone = 50:1).
Yield: 1.86 g (47.7% of theory),
M.p.: 113–116°C (ethanol)

Calc.:	C 73.44	H 7.19	N 7.14	m/e = 392
Found:	72.95	6.98	7.22	m/e = 392

Analogously to Example 6 the following compounds were prepared:

4-[(1-(6-Chloro-2-piperidino-phenyl)-ethenyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 37% of theory,
M.p.: 102–105°C

Calc.:	C 67.51	H 6.37	Cl 8.30	N 6.56	m/e = 426/28
Found:	67.86	6.39	8.58	6.23	m/e = 426/28

4-[(1-(6-Methyl-2-piperidino-phenyl)-ethenyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 41% of theory,
M.p.: 116–118°C

Calc.:	C 73.86	H 7.43	N 6.89
Found:	73.75	7.43	6.77

Example 7

4-[(1-(2-Piperidino-phenyl)-ethenyl)-aminocarbonylmethyl]benzoic acid ethyl ester

A solution of 1.55 g (6.86 m mol) of 4-ethoxycarbonylphenacetyl chloride in 5 ml of methylene chloride was added with stirring to a suspension of 2.20 g (6.24 m mol) of magnesium iodide-[methyl-(2-piperidino-phenyl)-ketimino]-complex in 15 ml of methylene chloride, whereby the internal temperature rose from 20 to 30°C. After stirring for 2 hours at room temperature, the reaction mixture was mixed with water whilst stirring and extracted several times with methylene chloride. The methylene chloride solution was washed thrice with water, dried over sodium sulfate, filtered and evaporated *in vacuo*. The evaporation residue was purified by column chromatography on silica gel (toluene/acetone = 50:2).
Yield: 1.1 g (45.8% of theory),
M.p.: 115–118°C (ethanol)

Calc.:	C 73.44	H 7.19	N 7.14
Found:	73.30	7.06	7.16

Analogously to Example 7 the following compound was prepared:

4-[(1-(5-Chloro-2-piperidino-phenyl)-ethenyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 39.5% of theory,
M.p.: 142–145°C (ethanol)

Calc.:	C 67.51	H 6.37	Cl 8.30	N 6.56
Found:	67.51	6.37	8.36	6.49

Example 8

4-[(1-(5-Chloro-2-dimethylamino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid

A solution of 2.0 g (0.00534 mol) of 4-[(1-(5-chloro-2-dimethylamino-ph nyl)-ethyl)-aminocarbonylmethyl]benzoic acid-methyl ester and 0.32 g (0.00801 mol) of sodium hydroxid in 23 ml of ethanol and 7 ml of water was stirred for 2 hours at 50°C. After vaporating *in vacuo*, water was added and the reaction mixture was adjusted to pH 6 by means of 2 N-hydrochloric acid and xtracted with ethyl acetate. The organic phase was extract d with water, dried over sodium sulfate, filtered and evaporated *in vacuo*. The vaporation residue was recrystallized from ether.

Yield: 1.7 g (88% of theory),
M.p.: 190–192°C

	C	H	Cl	N
Calc.:	63.24	5.87	9.83	7.76
Found:	62.90	5.81	10.02	7.90

Analogously to Example 8 the following compounds were prepared:

4-[(1-(5-Chloro-2-dipropylamino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 87.6% of theory,
M.p.: 203–205°C

	C	H	Cl	N
Calc.:	66.25	7.01	8.50	6.72
Found:	65.97	6.96	8.52	6.55

4-[(1-(5-Chloro-2-dibutylamino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 77.3% of theory,
M.p.: 200–202°C

	C	H	Cl	N
Calc.:	67.47	7.48	7.97	6.30
Found:	67.45	7.60	8.28	6.44

4-[(1-(5-Chloro-2-N-cyclohexyl-N-methylamino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 88.2% of theory,
M.p.: 198–200°C (ether).

	C	H	Cl	N
Calc.:	67.20	6.81	8.27	6.53
Found:	67.10	6.73	8.16	6.47

4-[(5-Chloro-2-pyrrolidino-benzyl)-aminocarbonylmethyl]benzoic acid
Yield: 84.2% of theory,
M.p.: 208–210°C (ethyl acetate)

	C	H	Cl	N
Calc.:	64.42	5.68	9.51	7.51
Found:	64.70	5.68	9.58	7.60

4-[(1-(5-Chloro-2-pyrrolidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 81.1% of theory,
M.p.: 202–204°C (ethyl acetate)

	C	H	Cl	N
Calc.:	65.20	5.99	9.17	7.24
Found:	65.02	6.12	9.32	7.10

4-[(5-Chloro-2-piperidino-benzyl)-aminocarbonylmethyl]benzoic acid
Yield: 78% of theory,
M.p.: 164–166°C

	C	H	Cl	N
Calc.:	65.19	5.99	9.17	7.24
Found:	65.50	5.76	9.24	7.36

4-[(1-(5-Chloro-2-piperidino-benzyl)-aminocarbonyl)-ethyl]benzoic acid
Yield: 81.1% of theory,
M.p.: 213–216°C (acetone/ether)

	C	H	Cl	N
Calc.:	65.90	6.29	8.84	6.99
Found:	66.30	6.40	9.00	7.04

4-[(1-(5-Chloro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 84.9% f theory,
M.p.: 213–215°C (eth r)

	C	H	Cl	N
Calc.:	65.91	6.29	8.85	6.99
Found:	66.18	6.19	8.88	7.12

4-[(1-(5-Chloro-2-(3-methyl-piperidino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 69.2% f theory,
M.p.: 208–210°C (ethyl acetate)

	C	H	Cl	N
Calc.:	66.57	6.56	8.55	6.75
Found:	66.36	6.77	8.58	6.80

4-[(1-(5-Chloro-2-(3,5-cis-dimethyl-piperidino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 82.2% of theory,
M.p.: 212–214°C (ether)

	C	H	Cl	N
Calc.:	67.20	6.81	8.26	6.53
Found:	66.95	6.69	8.43	6.68

4-[(1-(5-Chloro-2-piperidino-phenyl)-propyl)-aminocarbonylmethyl]benzoic acid
Yield: 81.5% of theory,
M.p.: 200–203°C (ether)

	C	H	Cl	N
Calc.:	66.57	6.56	8.55	6.75
Found:	66.74	6.35	8.59	6.45

4-[(1-(5-Chloro-2-piperidino-phenyl)-2-methyl-propyl)-aminocarbonylmethyl]benzoic acid
Yield: 82.7% of theory,
M.p.: 236–240°C (ethyl acetate)

	C	H	Cl	N
Calc.:	67.20	6.81	8.27	6.53
Found:	67.19	6.56	8.14	6.39

4-[(1-(5-Chloro-2-morpholino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 85.6% of theory,
M.p.: 201–203°C (ether)

	C	H	Cl	N
Calc.:	62.60	5.75	8.80	6.95
Found:	62.30	5.82	8.83	6.85

4-[(1-(5-Chloro-2-thiomorpholino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 87.6% of theory,
M.p.: 216–217°C (ether)

	C	H	Cl	N
Calc.:	60.20	5.53	8.46	6.69
Found:	59.90	5.51	8.61	6.53

4-[(1-(5-Chloro-2-(hexahydro-1H-azepino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 81.2% of theory,
M.p.: 202–204°C (chloroform/toluene)

	C	H	Cl	N
Calc.:	66.58	6.56	8.55	6.75
Found:	66.60	6.37	8.50	6.59

4-[(1-(5-Chloro-2-octahydroazocino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 44.4% of theory,
M.p.: 195–197°C (chloroform/petroleum ether)

	C	H	N
Calc.:	67.19	6.81	6.53
Found:	67.10	6.97	6.37

4-[(1-(5-Chloro-2-(octahydro-1H-azonino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 74.7% of theory,
M.p.: 204–206°C (ethyl acetate/petroleum ether)

	C	H	N
Calc.:	67.78	7.05	6.32
Found:	67.50	7.03	6.04

4-[(2-(5-Chloro-2-piperidino-phenyl)-2-propyl)-aminocarbonylmethyl]benzoic acid
Yield: 82.9% of theory,
M.p.: 227–229°C (acetone)

Calc.:	C 66.57	H 6.56	Cl 8.55	N 6.75
Found:	66.03	6.66	8.67	6.59

4-[(1-(5-Nitro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 95.6% of theory,
M.p.: 252–254°C (ether)

Calc.:	C 64.22	H 6.12	N 10.21
Found:	64.20	6.17	10.12

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 85% of theory,
M.p.: 170–172°C

Calc.:	C 72.11	H 7.15	N 7.64
Found:	71.94	7.03	7.72

4-[(2-(2-Piperidino-phenyl)-2-propyl)-aminocarbonylmethyl]benzoic acid
Yield: 72.7% of theory,
M.p.: 213–215°C

Calc.:	C 72.61	H 7.42	N 7.36
Found:	72.52	7.31	7.45

4-[(5-Methyl-2-piperidino-benzyl)-aminocarbonylmethyl]benzoic acid
Yield: 64.6% of theory,
M.p.: 120–122°C

Calc.:	C 72.11	H 7.15	N 7.64	m/e = 366
Found:	72.42	7.38	7.45	m/e = 366

M.p. of the hydrochloride: 266°C (decomp.)

Calc.:	C 65.58	6.76	8.80	N 6.95
Found:	65.00	6.62	9.40	7.00

4-[(2-Piperidino-anilino)-carbonylmethyl]benzoic acid × 0.25 HCl
Yield: 72.5% of theory,
M.p.: 216–217°C

Calc.:	(X 0.25 HCl)C 69.11		H 6.45	Cl 2.55	N 8.06
Found:	69.40		6.32	3.08	8.37

4-[(5-Chloro-2-piperidino-anilino)-carbonylmethyl]benzoic acid hydrochloride
Yield: 51.3% of theory,
M.p.: 232°C (decomp.)

Calc.:	C 58.68	H 5.42	Cl 17.32	N 6.84
Found:	58.26	5.44	17.97	6.74

4-[2-(2-Piperidino-anilino-carbonyl)-ethyl]benzoic acid semihydrate
Yield: 69.9% of theory,
M.p.: 151–153°C (petroleum eth r/aceton)

Calc.:	(× 0.5 H_2O)	C 69.78	H 6.97	N 7.75
Found:		69.30	6.82	7.46

4-[2-(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonyl)-ethyl]benzoic acid × 0.2 H_2O
Yield: 71.4% of theory,
M.p.: 171–172°C (acet n /petrol um ether)

Calc.:	(× 0.2 H_2O)	C 71.91	H 7.45	N 7.29
Found:		71.90	7.30	7.03

Example 9

4-[(1-(5-Benzyloxy-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid

244 mg (0.487 m mol) of 4-[(1-(5-benzyloxy-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester in 2.5 ml of ethanol were heated with stirring with 0.73 ml of 1N sodium hydroxide solution in a bath of 50°C, until (after 3 hours) no ester could be detected in the thinlayer chromatogram. After addition of 0.73 ml of 1N hydrochloric acid, the reaction mixture was evaporated *in vacuo* and distributed between ethyl acetate and water. The organic xtract was dried over sodium sulfate, filtered and evaporated *in vacuo*. The evaporation residue was recrystallized from methanol.

Yield: 191 mg (83% of theory),
M.p.: 220–222°C

Calc.:	C 73.71	H 6.83	N 5.93
Found:	73.21	6.67	5.80

Analogously to Example 9 the following compounds were prepared:

4-[1-(2-Hexahydroazepino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 68.5% of theory,
M.p.: 174–176°C (ethyl acetate)

Calc.:	C 72.61	H 7.42	N 7.36
Found:	72.36	7.34	7.38

4-[(1-(2-(1,2,3,6-Tetrahydro-pyridino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 68.2% of theory,
M.p.: 158–160°C (ethyl acetate)

Calc.:	C 72.51	H 6.64	N 7.69
Found:	72.20	6.66	7.74

4-[(2-(5-Chloro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 75% of theory,
M.p.: 192–195°C (ethyl acetate)

Calc.:	C 65.91	H 6.29	Cl 8.84	N 6.99
Found:	66.39	6.17	8.45	6.78

4-[(1-(5-Fluoro-2-piperidino-phenyl)-ethyl]-aminocarbonylmethyl]benzoic acid
Yield: 52.9% of theory,
M.p.: 174–176°C (ethyl acetate)

Calc.:	C 68.73	H 6.55	N 7.29
Found:	68.30	6.48	7.45

4-[(5-Methyl-2-piperidino-benzyl)-aminocarbonylmethyl]benzoic acid
Yield: 53.9% of theory,
M.p.: 120–122°C (ethanol)

Calc.:	C 72.11	H 7.15	N 7.64	m/e = 366
F und:	72.45	7.04	7.65	m/e = 366

4-[(1-(5-Cyano-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yi ld: 71.6% of theory,
M.p.: 198–200°C (eth r)

	C	H	N
Calc.:	70.57	6.44	10.73
Found:	70.17	6.38	11.00

4-[(1-(5-Carboxy-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid

Prepared from the corresponding diethyl ester by saponification with 2.5 equivalents of sodium hydroxide.
Yield: 73.5% of theory,
M.p.: 260°C (decomp.)

	C	H	N
Calc.:	67.30	6.38	6.82
Found:	67.76	6.62	6.85

4-[(1-(2-[1,4-Dioxa-8-azaspiro[4.5]decane-8-yl]phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid semihydrate
Yield: 85.7% of theory,
M.p.: 130–135°C (petroleum ether/acetone)

		C	H	N
Calc.:	(× 0.5 H_2O)	66.49	6.74	6.46
Found:		66.56	6.65	6.46

4-[2-Hydroxy-1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 65% of theory,
M.p.: 155–157°C (decomp) (petroleum ether/ + acetone
Calc.: m/e = 382
Found: m/e = 382

4-[(1-(5-Chloro-2-(2-methyl-piperidino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 64.1% of theory.
M.p.: 195–198°C (ethyl acetate)

	C	H	Cl	N
Calc.:	66.57	6.56	8.54	6.75
Found:	66.01	6.25	8.32	6.90

4-[(1-(5-Aminocarbonyl-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 86% of theory,
M.p.: 231–235°C (ethyl acetate)

	C	H	N
Calc.:	67.46	6.65	10.26
Found:	67.96	6.68	10.11

4-[(1-(2-(4-Methyl-piperidino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 67.7% of theory,
M.p.: 173–175°C (chloroform)

	C	H	N
Calc.:	72.61	7.42	7.36
Found:	72.20	7.36	7.45

4-[(1-(2-Piperidino-phenyl)-ethyl)-N-methylaminocarbonylmethyl]benzoic acid hydrochloride
Conversion of the viscous betain (72% crude) into the hydrochloride by means of hydrochloric acid in isopropanolic solution.
Yield: 32% of theory,
M.p.: 222–230°C (decomp.) (ethanol)

	C	H	Cl	N
Calc.:	66.25	7.01	8.50	6.71
F und:	66.07	6.37	8.37	6.58

2-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 7% f theory,
M.p.: 135°C (decomp.)

Calc.:	C 72.10	H 7.15	N 7.64
Found:	72.29	7.03	7.37

3-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 86% of theory,
M.p.: 205–207°C

Calc.:	C 72.11	H 7.15	N 7.64
Found:	72.30	7.29	7.71

3-Chloro-4-[(1-(2-piperidino-phenyl)-ethyl)-amino-carbonylmethyl]benzoic acid
Yield: 38% of theory,
M.p.: from 175°C sintering, from 190°C clear melt

Calc.:	C 65.91	H 6.29	Cl 8.84	N 6.99
Found:	65.42	6.32	9.05	6.77

4-[(1-(2-(1,2,3,4-Tetrahydro-isoquinoline-2-yl)-phenyl)-ethyl)-aminocarbonylmethyl)benzoic acid
Yield: 59% of theory,
M.p.: 207–209°C

Calc.:	C 75.34	H 6.32	N 6.76
Found:	75.30	6.29	6.67

4-[(1-(3-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 33% of theory,
M.p.: 206–208°C

Calc.:	C 72.09	H 7.15	N 7.64
Found:	72.04	7.14	7.57

4-[(1-(6-Chloro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 35% of theory,
M.p.: 148–150°C

Calc.:	C 65.91	H 6.28	Cl 8.84	N 6.98
Found:	65.45	6.36	9.63	6.84

4-[(1-(6-Methyl-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 33% of theory,
M.p.: 170°C

Calc.:	C 72.60	H 7.41	N 7.36
Found:	72.45	7.34	7.32

4-[(1-(2-(Octahydro-isoindole-2-yl)-phenyl)-ethyl)-aminocarbonyl]benzoic acid
Yield: 64% of theory,
M.p.: 130°C

Calc.:	C 73.85	H 7.43	N 6.89
F und:	73.60	7.47	6.72

4-[(1-(2-Decahydro-isoquinoline-2-yl)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 71% of theory.
M.p.: 220–221°C

Calc.:	C 74.25	H 7.66	N 6.66	m/e = 420
Found:	74.45	7.50	6.58	m/e = 420

4-[(1-(2-(1,2,3,4,5,6,7,8-Octahydro-isoquinoline-2-yl)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 99% of theory,
M.p.: 70°C (decomp.)

Calc.:	(× 0,5 H_2O)	C 73.05	H 7.30	N 6.54	m/e = 418
Found:		73.00	7.16	5.98	m/e = 418

4-[(1-(4-Chloro-2-pipeidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 82.1% of theory,
M.p.: 200–202°C

Calc.:	C 65.91	H 6.29	Cl 8.84	N 6.99
Found:	66.06	6.40	9.01	6.93

4-[(1-(4-Methyl-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 66.5% of theory,
M.p.: 110–115°C

Calc.:	C 72.60	H 7.42	N 7.36
Found:	72.50	7.52	7.46

4-[(2-Piperidino-benzhydryl)-aminocarbonylmethyl]benzoic acid
Yield: 88% of theory,
M.p.: 232–234°C

Calc.:	C 75.68	H 6.59	N 6.54
Found:	75.16	6.52	6.74

4-[(5-Chloro-2-piperidino-benzhydryl)-aminocarbonylmethyl]benzoic acid
Yield: 78.5% of theory,
M.p.: 255–260°C

Calc.:	C 70.05	H 5.88	Cl 7.66	N 6.05
Found:	70.50	5.76	7.36	6.06

4-[(1-(4-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 81% of theory,
M.p.: 208–210°C

Calc.:	C 72.11	H 7.15	N 7.64
Found:	72.24	7.26	7.54

4-[(1-(2-(4-Methyl-piperazino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 65% of theory,
M.p.: 150–153°C

Calc.:	C 69.27	H 7.13	N 11.02	
Found:	69.62	7.65	10.64	

4-[(1-(2-(4-Benzyl-piperazino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid hydrochloride
Yield: 32% of theory,
M.p.: 180°C

Calc.:	C 68.07	H 6.53	Cl 7.18	N 8.51
Found:	67.85	6.56	7.18	8.51

4-[(1-(2-(4-p-Chlorophenyl-piperazino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 75% of theory,
M.p.: 212°C (decomp.)

Calc.:	C 67.84	H 5.90	Cl 7.42	N 8.79
Found:	67.74	6.22	7.59	8.82

4-[(α-Cyclohexyl-2-piperidino-benzyl)-aminocarbonylmethyl]benzoic acid
Yield: 33% of theory,
M.p.: 199–202°C

Calc.:	C 74.62	H 7.89	N 6.45
Found:	74.60	7.54	6.66

(+)-4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid × 0.3 H_2O
Yield: 40% of theory,
M.p.: 107°C (decomp. (isopropanol/ether)
$[\alpha]_D^{20} = +7.3°$ (c = 1; methanol)

Calc.:	(× 0.3 H_2O)	C 71.02	H 7.25	N 7.52	m/e = 366
Found:		70.90	7.22	7.42	m/e = 366

(−)-4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid sodium salt
Crude yield of betain: 77% of theory,

Calc.:	m/e = 366
Found:	m/e = 366

Conversion into the sodium salt by means of 1 equivalent of sodium hydroxide solution in ethanol.
M.p. of the sodium salt: 190°C (decomp.)

4-[(1-(2-Piperidino-phenyl)-ethenyl)-aminocarbonylmethyl]benzoic acid
Yield: 53.6% of theory,
M.p.: 158–160°C (ethanol)

Calc.:	C 72.51	H 6.64	N 7.69
Found:	72.40	6.34	7.51

4-[(1-(5-Chloro-2-piperidino-phenyl)-ethenyl)aminocarbonylmethyl]benzoic acid
Yield: 78.7% f theory,
M.p.: 198–200°C (acetone)

Calc.:	C 66.24	H 5.81	Cl 8.88	N 7.02
Found:	65.74	5.72	9.37	7.10

4-[(α-Cyclohexylidene-2-piperidino-benzyl)-aminocarbonylmethyl]benzoic acid
Yield: 21% of theory,
M.p.: 213–216°C

Calc.:	C 74.97	H 7.46	N 6.48
Found:	74.73	7.52	6.48

4-[(1-(6-Chloro-2-piperidino-phenyl)-ethenyl)-aminocarbonylmethyl]benzoic acid
Yield: 39% of theory,
M.p.: 162°C

Calc.:	C 66.24	H 5.81	Cl 8.88	N 7.02	m/e = 398/400
Found:	66.48	5.84	8.88	6.85	m/e = 398/400

4-[(1-(6-Methyl-2-piperidino-phenyl)-ethenyl)-aminocarbonylmethyl]benzoic acid
Yield: 49% of theory,
M.p.: 128–130°C

Calc.:	m/e = 378
Found:	m/e = 378

4-[(1-(2-Piperidino-phenyl)-propenyl)-aminocarbonyl)methyl]benzoic acid
Yield: 65% of theory,
M.p. (Z-form): 185–187°C (ethyl acetate)

Calc.:		C 72.99	H 6.92	N 7.40
Found:	(Z-form)	73.10	6.99	7.56

M.p. (E-form): 108–110°C

4-[(1-(5-Hydroxy-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid semihydrate
Saponification with 2.5 equivalents of sodium hydroxide.
Yield: 55.9% of theory,
Foam (from ether)

Calc.:	(× 0.5 H_2O)	C 67.50	H 6.95	N 7.16
Found:		67.11	7.15	6.87

4-[(1-(2-(2-Methyl-pyrrolidino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 62% of theory,
M.p.: 169–172°C

Calc.:	C 72.11	H 7.15	N 7.64
Found:	71.96	6.82	7.51

4-[(1-(5-Aminosulfonyl-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yi ld: 19.2% f theory,
M.p.: 210°C (decomp.)

Calc.:	C 59.30	H 6.11	N 9.43	m/ = 445
Found:	58.80	5.87	9.06	m/e = 445

4-[(1-(2-Piperidino-phenyl)-propyl)-aminocarbonylmethyl]benzoic acid
Yield: 71.4% of theory,
M.p.: 208–210°C (thanol)

Calc.:	C 72.61	H 7.42	N 7.36
Found:	72.30	7.44	7.45

Example 10

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid

A solution of 13.5 g (0.338 mol) of sodium hydroxide in 50 ml of water was added to 88.8 g (0.225 mol) of 4-[(1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester in 890 ml of ethanol and the mixture was stirred at an internal temperature of 60°C until no starting product could be detected in the thinlayer chromatogram (approx. 45 minutes). After adding 400 ml of water the reaction mixture was adjusted at 25°C to pH = 5.8 (using a pH meter) by means of semi-concentrated hydrochloric acid. After a short time crystallization began. After standing over-night at 20°C, the precipitate was filtered off and the crystals obtained were washed several times with water. Subsequently, the crystals were dissolved in methylene chloride and washed with a little water. After drying the organic phase over sodium sulfate, the solution was filtered and the solvent was removed *in vacuo*, whereby a solid evaporation residue of 57.5 g was obtained.

The ethanolic hydrochloric filtrate (pH = 5.8) was adjusted to pH = 5.0 by means of semi-concentrated hydrochloric acid, then the ethanol was distilled of *in vacuo* and the evaporated solution was cooled in ice. The resultant precipitate was filtered off, dissolved in methylene chloride, separated from the aqueous phase, the methylene chloride solution was dried, filtered and evaporated *in vacuo*. The solid evaporation residue obtained was 13.0 g. Both evaporation residues (together 70.5 g) were recrystallized from the 5-to 6-fold amount of ethanol/water (80/20) under addition of activated charcoal.

Yield: 62% of theory,
M.p.: 163–164°C

Calc.:	C 72.11	H 7.15	N 7.64
Found:	72.13	7.25	7.75

If on completion of the saponification, after the addition of water and cooling to 25°C immediately the pH is adjusted to 5.0, and then continued as described above, 75.9% of the dried evaporation residue may be obtained without further processing the ethanolic hydrochloric filtrate, which even before the final recrystallization gave a correct elementary analysis.

M.p.: 172–176°C

Calc.:	C 72.11	H 7.15	N 7.64
Found:	71.90	7.08	7.52

Analogously to Example 10 the following compounds were prepared:

4-[(1-(5-Methyl-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 56.6% of theory,
M.p.: 215–217°C (ethanol)

Calc.:	C 72.61	H 7.42	N 7.36
Found:	72.71	7.49	7.25

4-[(α-Carboxy-2-piperidino-benzyl)-aminocarbonylmethyl]benzoic acid × 0.66 H_2O

Prepared by saponification of the 4-[(α-methoxycarbonyl-2-piperidino-benzyl)-aminocarbonyl-methyl]benzoic acid ethyl ester with 2.5 equivalents of sodium hydroxide.
Yield: 72.2% of theory,
M.p.: 235–240°C (decomp.) (methanol/chloroform)

Calc.:	(× 0.66 H_2O)	C 64.69	H 6.33	N 6.85
Found:		64.64	6.23	6.61

Example 11

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid sodium salt monohydrate

500 mg (1.26 m mol) f 4-[(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester in 5 ml f ethan l w r stirred together with 1.26 ml of 1N sodium hydroxid solution for 1 hour at 50°C. After cooling to 0°C, the precipitated crystals were filtered off and washed with cold ethanol and with ether.
Yield: 238 mg (48.6% of theory),
M.p.: 245–250°C

Calc.:	(× 1 H_2O)	C 65.01	H 6.69	N 6.89
Found:		65.40	6.83	6.72

Analogously to Example 11 the following compound was prepared:

4-[(1-(5-Methoxy-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid sodium salt monohydrate
Yield: 17.5% of theory,
M.p.: 212–215°C

Calc.:	(× 1 H_2O)	C 63.28	H 6.70	N 6.42
Found:		63.20	6.82	6.51

From the sodium salt was obtained analogously to Example 9 the corresponding *acid as monohydrate:*
M.p.: 187–189°C (ethanol/water)

Calc.:	(× 1 H_2O)	C 66.40	H 7.29	N 6.76
Found:		66.87	6.97	6.80

Example 12
4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid sodium salt × 0.6 H_2O

8.4 g (0.0229 mol) of 4-[(1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid were dissolved at 60 to 65°C in 80 ml of ethanol. To this solution 22.9 ml of 1N sodium hydroxide solution were added with stirring and stirring was continued for 30 minutes. After cooling to 20°C. a precipitate was obtained. After cooling to 0°C, the precipitate was filtered and washed with cold ethanol and ether. The precipitate thus obtained, of m.p. 250–251°C, was recrystallized from ethanol/water (7/3).
Yield: 7.2 g (78.6% of theory),
M.p.: 253–255°C

Calc.:	(× 0.6 H_2O):	C 66.18	H 6.61	N 7.02
Found:		66.10	6.64	7.13

Example 13
4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid

100 mg (0.237 m mol) of 4-[(1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid-tert.butyl ester in 5 ml of benzene were heated together with some crystals of p-toluene sulfonic acid hydrate to reflux temperature for half a day. According to the thinlayer chromatogram then no starting product could be detected, and according to the R_f-value and mass spectrum the desired product was formed.
M.p.: 163–165°C

Calc.: m/e = 366
Found: m/e = 366

Example 14
4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid

0.46 g (1 m m l) of 4-[(1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]b nzoic acid benzyl ester in 20 ml of ethanol wer hydrogenated at 0.25 g of palladium/charcoal at 50°C and a hydrogen pressure of 5 bar. Aft r 5 hours the catalyst was filtered ff ver celit and the filtrate was evaporated *in vacuo*. Th evap ration residue was recrystallized fr m ethanol/water (8/2).
Yield: 0.26 g (71% of theory),
M.p.: 163–165°C

Calc.:	C 72.11	H 7.15	N 7.64
Found:	72.30	7.25	7.81

Example 15

4-[(1-(5-Chloro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid

2.54 g (0.02 mol) of oxalyl chloride were dropped at 0 to 5°C to a stirred solution of 3.57 g (0.01 mol) of N-[(1-(5-chloro-2-piperidino-phenyl)-ethyl]-N-[phenacetyl]amine in 16 ml of carbon disulfide and subsequently 2.67 g (0.02 mol) of aluminium chloride were added. After one hour again the same amounts of oxalyl chloride and aluminium chloride were added and the mixture was heated subsequently for 3 hours up to 50°C. After cooling, ice water and hydrochloric acid were added and the reacting mixture was extracted with chloroform. The organic extract was dried and filtered and evaporated *in vacuo*. The evaporation residue was purified by column chromatography on silica gel (chloroform/methanol = 10:1).
Yield: 0.60 g (15% of theory),
M.p.: 213–214°C (ether)

Calc.:	C 65.91	H 6.29	Cl 8.85	N 6.99
Found:	66.13	6.05	8.97	7.25

Example 16

N-[4-Acetyl-phenacetyl]-N-[1-(5-chloro-2-piperidino-phenyl)-ethyl]amine

A solution of 0.6 ml (8.43 m mol) of acetyl chloride in 5 ml of methylene chloride was added at an internal temperature of 0 to 5°C to 1.12 g (8.43 m mol) of aluminium chloride in 10 ml of methylene chloride. Subsequently, at 0 to 5°C, a solution of 1 g (2.81 m mol) of N-[1-(5-chloro-2-piperidinophenyl)-ethyl]-N-[phenacetyl]amine in 5 ml of methylene chloride was added with stirring. The reaction mixture was stirred for 1 hour at 3°C and for 2 days at 20°C. After decomposing under cooling with ice water and hydrochloric acid, the methylene chloride phase was separated and the aqueous phase was extracted with chloroform. The combined oganic phases were dried over sodium sulfate, filtered and evaporated *in vacuo*. The evaporation residue was purified by column chromatography on silica gel (toluene/acetone = 4:1).
Yield: 0.28 g (25% of theory),
M.p.: 160–161°C

Calc.:	C 69.24	H 6.82	Cl 8.89	N 7.02	m/e = 398/400
Found:	69.55	6.99	9.45	6.85	m/e = 398/400

Example 17

4-[(1-(5-Chloro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid

A solution of 1.23 g (0.0031 mol) of N-[4-acetyl-phenacetyl]-N-[1-(5-chloro-2-piperidino-phenyl)-ethyl]amine in 12 ml of dioxan was added over 15 minutes at 35–40°C to a stirred sodium hypobromite solution [prepared from 1.84 g (0.046 mol) of sodium hydroxide, dissolved in 9 ml of water, and 0.72 ml (0.014 mol) of bromine under ice cooling]. After 40 minutes at 35–40°C aqueous sodium hydrogen sulfite solution and water was added and the mixture was evaporated *in vacuo*. The residue was dissolved with water, acidified under cooling with 2N hydrochloric acid and extracted with ether/ethyl acetate. The organic phase was dried and filtered, and evaporated *in vacuo*. The evaporation residue was recrystallized from ether.
Yield: 0.14 g (11% of theory),
M.p.: 213–215°C

Calc.:	C 65.91	H 6.29	Cl 8.85	N 6.99
Found:	65.78	5.98	8.95	7.17

Analogously to Example 17 the following compound was prepared:

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 15% of theory,
M.p.: 170–171°C

Calc.:	C 72.11	H 7.15	N 7.64
F und:	72.45	7.01	7.48

Example 18

4-[1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzaldehyde

Prepared from 4-[(1-(2-piperidino-ph nyl)-ethyl)-aminocarb nylmethyl]benzyl alcohol by oxidation with active manganese di xid in absolute acetone and subsequ nt purification by column

chromatography n silica gel (chloroform/acet n = 20:1).
Yield: 4% of theory,
Mp.:159°C

Calc.:	C 75.40	H 7.48	N 7.99
Found:	75.05	7.18	7.67

Example 19

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid

Prepared from 4-[(1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzaldehyde by heating with silver oxide in the presence of 1N sodium hydroxide solution for 20 minutes on a steam bath, subsequent acidification with 2N sulfuric acid at pH = 5, extraction with ethyl acetate and purification by column chromatography on silica gel (toluene/acetone = 1:1).
Yield: 3% of theory
Mp.: 168–170°C

Calc.: m/e = 366
Found: m/e = 366

Example 20

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester

5.5 g (0.014 mol) of 4-[(1-(2-piperidino-phenyl)-ethenyl)-aminocarbonylmethyl]benzoic acid ethyl ester in 110 ml of ethanol were hydrogenated at 1.5 g of palladium/charcoal (10%) at 20°C and a hydrogen pressure of 5 bar. After 30 minutes the catalyst was filtered off over celite and the filtrate was evaporated *in vacuo* to a volume of 20 ml. 100 ml of petroleum ether were adde and the mixture was cooled to 0°C.
Yield: 4.7 g (85.5% of theory),
M.p.: 152–154°C

Calc.:	C 73.07	H 7.66	N 7.10
Found:	72.80	7.63	7.08

Analogously to Example 20 the following compound was prepared:

4-[1-(2-Piperidino-phenyl)-propyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 70.8% of theory,
M.p.: 132–134°C

Calc.:	C 73.00	H 7.90	N 6.86
Found:	73.71	7.88	6.77

Example 21

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid

100 mg (0.2744 m mol) of 4-[(1-(2-piperidino-phenyl)-ethenyl)-aminocarbonylmethyl]benzoic acid in 5 ml of absolute ethanol were hydrogenated at 50 mg of palladium/charcoal (10%) at 20°C and at a hydrogen pressure of 1 bar under shaking. After 1.5 hours the catalyst was filtered off and the filtrate was evaporated *in vacuo*.
Yield: 91% of theory,
M.p.: 170–171°C

Calc.: m/e = 366
Found: m/e = 366

Example 22

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid semihydrate

200 mg (0.5014 m mol) f 4-[(1-(5-chloro-2-piperidinophenyl)-ethenyl)-aminocarbonylmethyl]-benzoic acid in 10 ml of absolut ethanol were hydrog nated at 100 mg of palladium/charcoal (10 %) at 50°C and at hydr gen pr ssur f 1 bar under shaking. After 1.5 hours the catalyst was filtered off, 5 ml of water were add d, adjusted to pH = 6 by m ans of 1N-sodium hydroxid solution and the thanol was evap rated *in vacuo*. A colourless precipitate was btained, which was filt red after c oling.
Yield: 100 mg (53.1% f theory),
M.p.: 135°C

Calc.:	(× 0.5 H_2O)	C 70.36	H 7.24	N 7.46	m/e = 366
Found:			70.31 7.44	7.78	m/ = 366

Example 23

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester

1.6 ml of conc. sulfuric acid were added in little drops to a mixture of 2 g (9.74 m mol) of 1-(2-piperidino-phenyl)-ethanol and 4 g (21.1 m mol) of 4-cyanomethyl-benzoic acid ethyl ester whilst stirring and cooling with ice by keeping the internal temperature at 35 to 40°C. Subsequently, the mixture was heated for 2.5 hours in a bath of 80°C, further 2 g (10.5 m mol) of 4-cyanomethyl benzoic acid ethyl ester and 0.8 ml of conc. sulfuric acid were added and heating was continued for 1 hour at 80°C and for 3 hours at 100°C. After that time no starting alcohol could be detected in the thinlayer chromatogram. After cooling to 20°C the mixture was extracted with ethyl acetate whilst stirring and cooling ice water was added. After extracting several times with ethyl acetate, the organic extract was dried over sodium sulfate, filtered and evaporated *in vacuo*. The evaporation residue was purified by column chromatography on silica gel (toluene/acetone = 10:1). From the pre-fractions 0.5 g of 2-piperidino-styrol were isolated.
Yield: 0.66 g (17.4% of theory),
M.p.: 147–150°C (ethanol)

Calc.:	C 73.07	H 7.66	N 7.10
Found:	73.26	7.55	6.90

Example 24

4-[(1-(5-Chloro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid

0.4 ml (5.55 m mol) of thionyl chloride were added to a stirred solution of 1 g (5.55 m mol) of 4-carboxy-phenylacetic acid and of 1.32 g (5.55 m mol) of (5-chloro-2-piperidino-phenyl)-ethylamine in 10 ml of absolute pyridine, whereby the internal temperature rised from 20°C to 35°C. The deep-brown reaction mixture was stirred for 3 hours at 20°C and evaporated *in vacuo*. The evaporation residue was distributed between water (at pH = 3 after addition of 2N hydrochloric acid) and chloroform. The organic extract was dried and filtered and evaporated *in vacuo*. The evaporation residue was purified by column chromatography on silica gel (chloroform/methanol = 10:1).
Yield: 1.06 g (48% of theory),
M.p.: 212–214°C (ether)

Calc.:	C 65.91	H 6.29	Cl 8.85	N 6.99
Found:	65.79	6.01	8.69	6.87

Analogously to Example 24 the following compounds were prepared:

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 52% of theory,
M.p.: 169–171°C

Calc.:	C 72.11	H 7.15	N 7.64
Found:	71.84	6.87	7.72

4-[(1-(2-(4-Oxo-piperidino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 32% of theory,
M.p.: 177–180°C (decomp.) (acetone/petroleum ether)

Calc.:	C 69.46	H 6.36	N 7.36
Found:	69.62	6.41	7.50

4-[(1-(2-(4-Hydroxy-piperidino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid × 0.66 H_2O
Yield: 23.5% of th ory,
M.p.: 176–179°C (decomp.) (acet ne/petrol um ether)

Calc.:	(× 0.66 H_2O)	C 66.97	H 6.81	N 7.10
Found:		67.12	6.78	7.26

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzonitrile
Prepared from 4-cyano-ph nyl acetic acid.
Yield: 51% of the ry,
M.p.: 155–157°C (ethyl acetate)

Calc.:	C 76.05	H 7.25	N 12.09
Found:	76.41	7.10	12.20

Example 25
4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzyl alcohol
Prepared from 4-[(1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester by lithium aluminium hydride reduction in tetrahydrofuran.
Yield: 39% of theory.
M.p.: 104–106°C

Calc.:	C 74.96	H 8.00	N 7.94
Found:	74.80	7.80	7.80

Example 26
4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzyl malonic acid diethyl ester
A solution of 3.7 g (10 m mol) of 4-[(1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzyl chloride [m.p.: 123–125°C; prepared from the alcohol described in Example 25 by means of thionyl chloride in chloroform] in 35 ml of absolute ethanol was added to a solution of sodium malonic acid diethyl ester [prepared from 0.7 g (30 m mol) of sodium in 25 ml of absolute ethanol and 4.8 (30 m mol) of malonic acid diethyl ester]. A catalytic amound of potassium iodide was added and the mixture was refluxed for 16 hours. After evaporating *in vacuo*, the evaporation residue was adjusted to neutral by means of hydrochloric acid and extracted with methylene chloride. The organic extract was dried over sodium sulfate, filtered and and evaporated *in vacuo*. The evaporation residue was purified by column chromatograph on silica gel (toluene/acetone = 6:1).
Yield: 3.0 g (60% of theory),
M.P: <20°C

Calc.:	m/e = 494
Found:	m/e = 494

Example 27
3-[4[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]-phenyl]propionic acid
5 ml of 1N-sodium hydroxide solution were added to a solution of 0.85 g (1.7 m mol) of 4-[(1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzyl malonic acid diethyl ester in 18 ml of ethanol. After stirring for 2 hours at 50°C, the mixture was evaporated *in vacuo*, and water and 5 ml of 1N-hydrochloric acid were added. The formed precipitate was filtered off, dried *in vaco* and heated for 30 minutes up to 120°C, whereby carbon dioxide was liberated. The product was purified by column chromatography on silica gel (chloroform/methanol = 20:1).
Yield: 0.15 g (22.2% of theory),
M.p.: 68–70°C

Calc.:	C 73.06	H 7.67	N 7.10	m/e = 394
Found:	72.64	7.42	6.81	m/e = 394

Example 28
4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzaldehyde
Prepared by heating crude N^1-[4-[(1-(2-piperidinophenyl)-ethyl)-aminocarbonylmethyl]benzoyl]-N^2-tosylhydrazine in anhydrous sodium carbonate at 160–170°C in ethylene glycol [prepared from 4-[(1-(2-piperidino-pheyl)-ethyl)-aminocarbonylmethyl]benzoic acid and tosyl-hydrazine with carbonyl diimidazole in tetrahydrofuran].
Yield: 10% f theory,
M.p.: 159°C

Calc.:	C 75.40	H 7.48	N 7.99
Found:	74.99	7.24	7.60

Example 29
4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
0.50 g (1.247 m m l) f 4-[(1-(5-chloro-2-piperidino-ph nyl)-ethyl)-amin carbonylmethyl]ben-

zoic acid in 20 ml of absolute ethanol were hydrogenated at 0.25 g of palladium/charcoal (10%) at 50°C and a hydrogen pressure of 5 bar. After 2 hours the catalyst was filtered off over celite and after evaporating *in vacuo* the residue was distributed at pH = 6 between water and ethyl acetate. The organic extract was washed with water, dried and filtered and evaporated *in vacuo*.
Yield: 0.31 g (67% of theory),
M.p.: 170–172°C (ether)

Calc.:	C 72.11	H 7.15	N 7.64
Found:	71.76	6.98	7.51

Analogously to Example 29 the following compounds were prepared:

4-[(2-(2-Piperidino-phenyl)-2-propyl)-aminocarbonylmethyl]benzoic acid
Yield: 68.5% of theory,
M.p.: 213–215°C

Calc.:	C 72.61	H 7.42	N 7.36
Found:	72.43	7.25	7.40

4-[(1-(2-Dimethylamino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 53.3% of theory,
M.p.: 165–168°C (acetone/petroleum ether)

Calc.:	C 69.92	H 6.79	N 8.59
Found:	69.88	6.83	8.49

4-[(2-Pyrrolidino-benzyl)-aminocarbonylmethyl]benzoic acid
Yield: 55% of theory,
M.p.: 212–215°C (methanol)

Calc.:	C 70.99	H 6.55	N 8.28
Found:	70.97	6.91	8.15

4-[(1-(2-Pyrrolidone-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 25% of theory,
M.p.: 155–157°C (acetone/ether)

Calc.:	C 71.57	H 6.86	N 7.95
Found:	71.22	6.75	8.42

4-[(2-Piperidino-benzyl)-aminocarbonylmethyl]benzoic acid
Yield: 60.4% of theory,
M.p.: 175–177°C (acetone)

Calc.:	C 71.57	H 6.86	N 7.95
Found:	71.48	7.00	8.09

4-[(2-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 60.4% of theory,
M.p.: 164–166°C (ethyl acetate)

Calc.:	C 72.11	H 7.15	N 7.64
Found:	72.35	7.18	7.76

4-[(1-(2-(2-Methyl-piperidino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 90.9% of theory,
M.p.: 171–173°C (petr leum ether/acetone)

Calc.:	C 72.61	H 7.42	N 7.36
Found:	72.30	7.39	7.43

4-[(1-(2-(3-Methyl-piperidino)-phenyl)-ethyl)-aminocarbonylmethyl/benzoic acid
Yield: 86.3% of theory,
M.p.: 170–173°C (petroleum ether/acetone)

Calc.:	C 72.61	H 7.42	N 7.36
Found:	72.20	7.28	7.12

4-[(1-(2-Dipropylamino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 51.1% of theory,
M.p.: 175–178°C (ethyl acetate)

Calc.:	C 72.22	H 7.91	N 7.32
Found:	72.10	8.05	7.69

4-[(1-(2-Piperidino-phenyl)-2-methyl-propyl)-aminocarbonylmethyl]benzoic acid
Yield: 86% of theory,
M.p.: 215–217°C (acetone)

Calc.:	C 73.06	H 7.67	N 7.10
Found:	73.10	7.55	6.99

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid methyl ester
Prepared from 4-[(1-(5-chloro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid methyl ester.
Yield: 37.2% of theory,
M.p.: 145–147°C

Calc.:	C 72.61	H 7.42	N 7.36
Found:	72.47	7.30	7.56

4-[(2-Piperidino-anilino)-carbonylmethyl]benzoic acid methylester
Prepared from 4-[(5-chloro-2-piperidino-anilino)-carbonylmethyl]benzoic acid methyl ester.
Yield: 60% of theory,
M.p.: 85–86°C (toluene/petroleum ether)

Calc.:	C 71.57	H 6.86	N 7.96
Found:	71.48	6.92	8.39

N-Phenacetyl-N-[1-(2-piperidiono-phenyl)-ethyl]amine
Prepared from N-[1-(5-chloro-2-piperidino-phenyl)-ethyl]-N-phenacetyl-amine.
Yield: 54.6% of theory,
M.p.: 120–121°C (petroleum ether/acetone)

Calc.:	C 78.22	H 8.13	N 8.69
Found:	77.90	8.24	8.75

Example 30
4-[(1-(5-Amino-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid methyl ester
2.0 g (0.0047 m l) f 4-[(1-(5-nitro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid methyl ester in 20 ml of dimethyl formamid w r hydrogenated at 0.2 g of palladium/-charcoal (10 %) in a Parr apparatus at 20°C and a hydrog n pressur of 1 bar. Wh n th

hydrogen absorption was finished (2 hours), the catalyst was filtered off over celite and evaporated to dryness *in vacuo*.
Yield: 1.8 g (95% of theory),
M.p.: 140–142°C (toluene).
Analogously to Example 30 the following compounds were prepared:

4-[(1-(5-Amino-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 97.8% of theory,
M.p.: 148–149.5°C (cyclohexane)

	C	H	N
Calc.:	70.39	7.63	10.26
Found:	70.20	7.67	9.60

4-[(1-(5-Amino-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Prepared from 4-[(1-(5-nitro-2-piperdino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid.
Yield: 85.7% of theory,
M.p.: 223–225°C (ether)

	C	H	
Calc.:	69.27	7.13	11.02
Found:	69.18	7.04	11.35

N-[4-Amino-phenacetyl]-N-[1-(2-piperidino-phenyl)-ethyl]-amine dihydrochloride semihydrate
Prepared from N-[4-nitro-phenacetyl]-N-[(1-(2-piperidinophenyl)-ethyl]amine. Conversion of the crude amino compound into the dihydrochloride in ethanol was by means of ethereal hydrochloric acid.
Yield: 17.5% of theory,
M.p.: 238°C (decomp.)

		C	H	Cl
Calc.:	(× 2 HCl × 0.5 H_2O)	60.12	7.21	16.91
Found:		60.52	7.52	17.05

Example 31
4-[(1-(5-Bromo-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
A solution of 0.072 g (1.05 m mol) of sodium nitrite in 0.5 ml of water was added at an internal temperature of 0 to 5°C to 0.40 g (1.05 m mol) of 4-[(1-(5-amino-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid in 2 ml of semi-conc. aqueous hydrobromic acid. The resultant diazonium salt solution was then added to 0.196 g of copper (I) bromide in 2 ml of 48% hydrobromic acid, whereby considerable formation of gas occurred. The reaction mixture was stirred for 1.5 hours at an internal temperature of 45–50°C, cooled and adjusted to pH 4 by means of 4N sodium hydroxide solution. After extraction with warm ethyl acetate, the extract was washed with water, dried and filtered. After evaporating *in vacuo*, the obtained residue was purified by column chromatography on silica gel (chloroform/methanol = 7:1).
Yield: 0.08 g (17% of theory),
M.p.: 212–213°C (ethyl acetate/petroleum ether)

	C	H	Br	N
Calc.:	59.32	5.66	17.94	6.29
Found:	59.30	5.71	17.85	6.48

Analogously to Example 31 the following compound was prepared:

4-[(1-(5-Chloro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Prepared by diazotization of 4-[(1-(5-amino-2-piperidinophenyl)-ethyl)-aminocarbonylmethyl]-benzoic acid in conc. HCl and Sandmeyer reaction with copper (I) chloride.
Yield: 25.2% of theory,
M.p.: 213–215°C

	C	H	Cl	N
Calc.:	65.91	6.29	8.85	6.99
Found:	66.20	6.31	8.87	6.82

If the reaction is carried out in hydrochloric acid without copper (I) chloride, a yield of 19% of theory is obtained. Furthermore, 9% of the corresponding 5-hydroxy compound is obtained.

Example 32

4-[(1-(5-Iodo-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester

A solution of 0.17 g (2.44 m mol) of sodium nitrite in 0.52 ml of water was slowly added at 0 to 5°C whilst stirring to 1.0 g (2.44 m mol) of 4-[(1-(5-amino-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester in 1.9 ml of semi-conc. hydriodic acid and the solution was warmed to 20°C over 1 hour. After heating for 2 hours at 100°C, the reaction mixture was cooled and extracted with ethyl acetate. The organic phase was washed with dilute sodium bicarbonate solution and with water, dried over sodium sulfate, filtered, and evaporated *in vacuo*. The evaporation residue was purified by column chromatography on silica gel (toluene/acetone = 5:1).

Yield: 0.011 g (0.93% of theory);
M.p.: 145–147°C (ether)

Calc.:	C 55.39	H 5.62	N 5.38	m/e = 520
Found:	55.95	5.53	5.05	m/e = 520

Example 33

4-[(1-(5-Cyano-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester

A solution of 0.34 g (4.88 m mol) of sodium nitrite in 2.3 ml of water was added, with stirring at −5 to 0°C, to 2.0 g (4.88 m mol) of 4-[(1-(5-amino-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester in 4.0 ml of water and 3.5 ml of conc. hydrochloric acid. The mixture was stirred for 15 minutes and then neutralized with 1.1 g of calcium carbonate. The suspension thus obtained was added by means of 2 × 15ml portions of water into a 0°C solution, which was prepared from 0.568 g (6.34 m mol) of copper (I) cyanide, 1.24 g (19 m mol) of potassium cyanide and 5.8 ml of water, whereby immediately a red-coloured precipitate was obtained. The reaction mixture was heated whilst stirring for 30 minutes at an internal temperature of 45°C, then for 30 minutes at 70°C and for 60 minutes at 95°C. The red-coloured spot was now no longer visible in the thinlayer chromatogram. The reaction mixture was cooled to 20°C and extracted with ethyl acetate. The organic extract was dried over sodium sulfate, filtered, and evaporated *in vacuo*. The evaporation residue was purified by two column chromatographies on silica gel ((a) toluene/acetone = 10:1, (b) methylene chloride/acetonitrile/glacial acetic acid = 10:1:0.05). Besides the corresponding 5-Cl- and 5-H-compounds, the 5-cyano compound was obtained.

Yield: 0.186 g (9% of theory),
M.p.: 165–167°C (ether)

Calc.:	C 71.58	H 6.97	N 10.02	m/e = 419
Found:	71.64	6.94	9.72	m/e = 419

Example 34

4-[(1-(5-Aminosulfonyl-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester

(a) A solution of 0.37 g (5.36 m mol) of sodium nitrite in 0.7 ml of water was added with stirring at 4 to 6°C to a suspension of 2.0 g (4.88 m mol) of 4-[(1-(5-amino-2-piperidino-phenyl)-aminocarbonylmethyl]benzoic acid ethyl ester in 2.02 ml of semi-conc. hydrochloric acid. Subsequently, 0.37 g (3.89 m mol) of magnesium chloride were added. The mixture thus obtained was dropped subsequently at 30°C to a solution, which was prepared from 4.9 ml of glacial acetic acid (saturated with sulfur dioxide) and 0.27 g of copper(II)chloride dihydrate. Thereby the internal temperature rose to 40°C and nitrogen was formed. After stirring for 15 minutes in a bath at 50°C, 7.5 ml of water were added and the mixture was extracted with chloroform. The organic extract was dried over sodium sulfate, filtered, and evaporated in vacuo. The viscous, red-brown evaporation residue (2.7 g; still chloroform-containing) contained besides the corresponding 5-chloro-compound the desired 4-[(1-(5-chlorosulfonyl-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester.

(b) A solution of the evaporation residue obtained according to Example a) in 10 ml of chloroform was added at 2°C whilst stirring to 50 ml of conc. ammonia. After 30 minutes saturated sodim chloride solution was added to obtain separation of the phases. After extracting with chlor form, the organic extract was dri d and filtered and evaporat d *in vacuo*. The evaporation residue was purified by column chromatography on silica gel (chloroform/methanol = 10:1). B sides 55% of the corresponding 5-chloro-compound the d sired 5-aminosulfonyl c mp und was btained as f am.

Yield: 32% of theory.

Calc.: m/ =473
Found: m/e=473

Example 35
4-[(1-(5-Dimethylamino-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid

10 g (1.589 m mol) of sodium-cyanoboro-hydride and after 2 minutes 0.056 ml of glacial acetic acid were added at 20°C to a stirred solution of 0.20 g (0.5242 m mol) of 4-[(1-(5-amino-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid and 0.45 ml of 40% formalin in 2 ml of aetonitrile and 1 ml of absolute dimethyl formamide. After 1.5 hours the reaction mixture was evaporated *in vacuo*. The evaporation residue was dissolved in water by addition of hydrochloric acid at pH 2–3. After several extractions with chloroform the aqueous phase was adjusted to pH 6 to 7 by means of saturated sodium hydrogen carbonate solution and further extracted several times with chloroform. This organic extract was dried and filtered. After evaporating *in vacuo* the evaporation residue was recrystallized from isopropanol. The colourless crystals were washed with absolute ether.
Yield: 0.09 g (42.8% of theory),
M.p.: 185°C (decomp. from 175°C)

Calc.:	C 70.39	H 7.63	N 10.26
Found:	70.10	7.63	10.47

Example 36
4-[(1-(5-Acetylamino-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid

0.10 g (0.262 m mol) of 4-[(1-(5-amino-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid in 1 ml of acetic anhydride were stirred for 6 hours at 20°C, then evaporated *in vacuo*, distilled off several times with toluene, and the evaporation residue was recrystallized from ether.
Yield: 0.08 g (72.7% of theory),
M.p.: 241–243°C

Calc.:	C 68.07	H 6.90	N 9.92
Found:	67.53	6.83	9.72

Example 37
4-[(1-(5-Benzoylamino-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid

0.30 ml (2.62 m mol) of benzoyl chloride were added to a solution of 1 g (2.62 m mol) of 4-[(1-(5-amino-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid and 0.37 ml (2.62 m mol) of triethylamine in 10 ml of anhydrous dimethyl formamide. After stirring for 2 hours at 20–30°C, the reaction mixture was evaporated *in vacuo* and distributed between water and ethyl acetate. The organic phase was dried and filtered and evaporated *in vacuo*. The evaporation residue (1.12 g) was recrystallized from ethanol by addition of activated charcoal.
Yield: 0.5 g (39.4% of theory),
M.p.: 225–224°C

Calc.:	C 71.73	H 6.43	N 8.65
Found:	71.70	6.50	8.66

Analogously to Example 37 the following compound was prepared:

4-[(1-(5-Ethoxycarbonylamino-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Yield: 34.2% of theory,
M.p.: 220°C (decomp.)

Calc.:	C 66.21	H 6.89	N 9.26
Found:	65.97	6.83	9.57

Example 38
4-[1-(5-Methylsulfonylamino-2-piperidino-phenyl)ethyl)-aminocarbonylmethyl]benzoic acid

0.20 ml (0.262 m mol) of mesyl chloride were added to a solution of 0.10 g (0.262 m m l) f 4-[(1-(5-amino-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid in 1 ml of anhydrous pyridine. After the exothermic reaction was finished the mixture was allowed to stand for 4 hours at 20°C. Subsequently the reacti n mixtur was evaporated *in vacuo* and the evaporation residue was distributed at pH 2–3 between wat r and chl roform. The acidic aqueous phase was adjust d to pH 6 to 7 by means of sodium hydrog n carbonate solution and

extracted with chloroform. This chloroform extract was dried and filtered. The residue obtained after evaporating *in vacuo* was purified by column chromatography on silica gel (chloroform/-methanol = 4:1).
Yield: 0.03 g (25% of the theory),
M.p.: 210–220°C (decomp.) (ether)

Calc.: mol peak . m/e = 459
Found: m/e = 459

Example 39
4-[(1-(5-Acetoxy-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
0.35 g (0.915 m mol) of 4-[(1-(5-hydroxy-2-piperidinophenyl)-ethyl)-aminocarbonylmethyl]-benzoic acid were heated together with 0.103 ml (1.098 m mol) of acetic anhydride on the steam bath and after standing for 4 days at 20°C, the reaction mixture was recrystallized from methanol.
Yield: 0.16 g (41.2% of theory),
M.p.: 218–221°C

Calc.:	C 67.91	H 6.65	N 6.60
Found:	67.70	6.95	6.55

Example 40
4-[(1-(5-Methoxy-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid methyl ester
A solution of 60 mg (0,157 m mol) of 4-[(1-(5-hydroxy-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid in 1 ml of methanol (+ 1 drop of water) was added dropwise to an ethereal diazomethane solution, until no formation of gas took place. To destroy excess diazomethane 2N acetic acid was added. After evaporating *in vacuo*, the evaporation residue was distributed between toluene/ether and dilute sodium hydroxide solution. After drying, filtering and evaporating the organic phase *in vacuo*, the evaporation residue was purified by column chromatography on silica gel (chloroform/methanol = 5:1).
Yield: 27% of theory,
M.p.: Foam

Cal.: mol/peak m/e = 410
Found: m/e = 410

Example 41
4-[(1-(5-Benzyloxy-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
A solution of 0.50 g (1.218 m mol) of 4-[(1-(5-hydroxy-2-piperidino-pheyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester in 10 ml of anhydrous dimethyl formamide was quickly added to a suspension of 1.353 m mol of sodium hydride (32.5 mg of a 50% suspension in oil) in 2 ml of anhydrous dimethyl formamide. After stirring for 1.5 hours at 20°C, 0.16 ml (1.353 m mol) of benzyl bromide, dissolved in 2.3 ml of anhydrous dimethyl formamide, were added and stirring was continued for 16 hours at 20°C. After evaporating *in vacuo* the residue was distributed between water and ether. The organic extract was dried, filtered and evaporated *in vacuo*. The evaporation residue was purified by column chromatography on silica gel (toluene/acetone = 10:1).
Yield: 0.34 g (55.5% of theory),
M.p.: 155–157°C (ether)

Calc.:	C 74.37	H 7.25	N 5.60
Found:	74.11	7.41	5.39

Example 42
4-[(1-(5-Aminocarbonyl-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
3.8 g (9.06 m mol) of 4-[(1-(5-cyano-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester and 38 g of polyphosphoric acid were stirred for 2.5 hours at 80–90°C. Under ice-cooling, water was added carefully and the reaction mixture was extracted with ethyl acetate and adjusted to alkaline by means of conc. ammonia. The organic phase was washed with water, dried and evaporated *in vacuo*. The evaporation residue was purified by column chromatography on silica gel (chloroform/methanol = 20/1).

Yield: 1 g (25.2% f th ory),
M.p.: 188–189°C (ethanol)

Calc.:	C 68.63	H 7.14	N 9.60
Found:	68.42	6.95	9.46

Example 43

4-[(1-(5-Ethoxycarbonyl-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester

Under reflux, dried hydrogen chloride was introduced into a solution of 1.1 g (2.62 m mol) of 4-[(1-(5-cyano-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester in 22 ml of absolute ethanol until after 4 hours no nitrile could be detected. The reaction mixture was evaporated *in vacuo*, mixed with water and ether, and adjusted to alkaline by means of sodium hydrogen carbonate solution. The separated ether phase was extracted with water, dried and filtered, and evaporated *in vacuo*. The evaporation residue was purified by column chromatography on silica gel (methylene chloride/acetonitrile/glacial acetic acid:10:1:0.05).
Yield: 0.6 g (49.2% of theory),
M.p.: 136–138°C (ether)

Calc.:	C 69.51	H 7.35	N 6.00
Found:	69.28	7.34	5.83

Example 44

4-[(1-(2-(4-Oxo-piperidino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid

A solution of 2.9 g (6.86 m mol) of 4-[(1-(2-[1,4-dioxa-8-aza-spiro[4.5]decane-8-yl]phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid semihydrate in 40 ml of acetone was adjusted to pH = 2 by the addition of 2N hydrochloric acid. After stirring for 6 hours at 50°C 5 drops of conc. hydrochloric acid were added and the mixture was allowed to stand for 16 hours at 20°C. The reaction mixture was evaporated *in vacuo*, mixed with water and ethyl acetate and adjusted to pH = 6 by means of 2N ammonia. After extracting several times with ethyl acetate, the combined organic extracts were washed with water, dried, filtered, and evaporated *in vacuo*. The evaporation residue was recrystallized from acetone/petroleum ether.
Yield: 1.9 g (73.1% of theory),
M.p.: 177–180°C (decomp.)

Calc.:	C 69.46	H 6.36	N 7.36
Found:	69.75	6.33	7.29

Example 45

4-[(1-(2-(4-Hydroxy-piperidino)-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid × 0.66 H_2O

0.244 g (5.92 m mol) of sodium boro-hydride were added in portions with stirring to a solution of 1 g (2.63 m mol) of 4-[(1-(2-(4-oxo-piperidino)-phenyl)-ethyl)-aminocarbonylmethyl]-benzoic acid in 20 ml of absolute ethanol. After stirring for 1.5 hours at room temperature, the reaction mixture was adjusted to acidic by means of 2N hydrochloric acid, evaporated *in vacuo*, mixed with water and ethyl acetate, and adjusted to pH = 6 by means of 2N sodium hydroxide solution. After extracting several times with ethyl acetate, the organic phase was dried, filtered, and the extract was evaporated *in vacuo*. The evaporation residue was recrystallized from petroleum ether.
Yield: 0.78 g (75% of theory),
M.p.: 175–180°C (decomp.)

Calc.:	(× 0.66 H_2O)	C 66.97	H 6.81	N 7.10
Found:		66.72	6.62	6.98

Example 46

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid propyl ester

0.94 g (5.80 m mol) of carbonyl diimidazole were added to a solution of 2 g (5.46 m mol) of 4-[(1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid in 20 ml of absolute tetrahydrofuran and the mixture was heated to reflux temperature for 30 minutes excluding moisture. Subsequently, 1.64 ml (2.2 m mol) of 1-propanol were added, the reaction mixture was stirred for 18 hours at 20°C and heated f r 8 hours to reflux temperature. After evaporating *in vacuo* th evaporation r sidue was purified by column chromatography on silica gel (toluen /acetone = 10:1).

Yield: 1.3 g (58.3% f theory),
M.p.: 150–151°C (ethyl acetate)

Calc.:	C 73.51	H 7.90	N 6.86
Found:	73.70	7.78	6.92

Analogously to Example 46 the following compounds were prepared:

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid isopropyl ester
Yield: 45% of theory,
M.p.: 141–143°C (ether)

Calc.:	C 73.51	H 7.90	N 6.86
Found:	73.20	7.79	6.70

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid butyl ester
Yield: 49% of theory,
M.p.: 148°C (ether/toluene)

Calc.:	C 73.90	H 8.11	N 6.63
Found:	74.10	7.99	6.70

4-[(1-(5-Chloro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid ethyl ester
Yield: 41% of theory,
M.p.: 130–133°C (ether)

Calc.:	C 67.21	H 6.81	Cl 8.26	N 6.53
Found:	66.90	6.65	8.32	6.67

4-[(1-(5-Chloro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid butyl ester
Yield: 30.7% of theory,
M.p.: 115–118°C

Calc.:	C 68.33	H 7.27	Cl 7.75	N 6.12
Found:	68.20	7.23	7.68	5.95

4-[(1-(5-Chloro-2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid tert.butyl ester
Yield: 1% of theory,

Calc.:	mol peak	m/e = 456/8
Found:		m/e = 456/8

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid-(2-methoxyethyl ester)
Yield: 56% of theory,
M.p.: 155–157°C (ethyl acetate)

Calc.:	C 70.74	H 7.60	N 6.60
Found:	70.55	7.38	6.47

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid]-(2,2-dimethyl-dioxolane-4-yl)-methyl]ester
Yield: 30.5% of theory,
M.p.: 110–112°C (ether)

Calc.:	C 69.98	H 7.55	N 5.83	m/ = 480
Found:	69.80	7.50	5.76	m/e = 480

4-[(1-(2-Piperidino-ph nyl)-ethyl)-aminocarbonylm thyl]benzoic acid b nzyl ester
Yi ld: 73.7% of theory,
M.p.: 126–128°C (ethyl acetate)

Calc.:	C 76.28	H 7.06	N 6.14	
Found:	76.33	7.20	6.03	

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid-(2-hydroxy-ethyl)-ester
After addition of 10 equivalents of ethylene glycol the reaction mixture was heated to reflux temperature for 17 hours.
Yield: 71.4% of theory,
M.p.: 128–129°C (ethyl acetate/ether)

Calc.:	C 70.21	H 7.36	N 6.82	m/e = 410
Found:	70.14	7.42	6.70	m/e = 410

1,2-Bis[4-[(1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoyloxy]ethane
After addition of 0.5 equivalents of ethylene glycol the reaction mixture was heated to reflux temperature for 17 hours.
Yield: 43.5% of theory,
M.p.: 188–191°C (toluene)

Calc.:	C 72.80	H 7.17	N 7.38	m/e = 758
Found:	72.85	7.07	7.37	m/e = 758

4[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid-(2-diethylamino-ethyl)-ester
Yield: 56.7% of theory,
M.p.: 99–101°C (petroleum ether)

Calc.:	C 72.23	H 8.44	N 9.03
Found:	72.40	8.37	8.95

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid-2-(1,3-dimethyl-xanthine-7-yl)-ethyl ester
As solvent absolute pyridine was used. After addition of 1 equivalent of 7-(2-hydroxy-ethyl)-theophylline and after addition of a little piece of metallic sodium the reaction mixture was stirred for 4 hours in the bath of 130°C.
Yield: 40.9% of theory,
M.p.: 121–123°C (ether)

Calc.:	C 65.01	H 6.34	N 14.68	m/e = 572
Found:	64.78	6.38	14.90	m/e = 572

Example 47
4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid methyl ester
A mixture of 2 g (5.46 m mol) of 4-[(1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid, 0.53 g of methanol, 0.38 ml of conc. sulfuric acid, and 1.65 ml of 1,2-dichloroethane was refluxed for 24 hours, then evaporated *in vacuo*, dissolved in chloroform, and extracted with diluted sodium hydrogen carbonate solution. The organic phase was washed with water, dried, filtered, and evaporated *in vacuo*. The evaporation residue was purified by column chromatography on silica gel (toluene/acetone = 5:1).
Yi ld: 0.93 g (44.8% f theory),
M.p.: 146–147°C

Calc.:	C 72.60	H 7.42	N 7.36
F und:	72.19	7.33	7.01

Example 48

4-[(2-(2-Piperidino-phenyl)-2-propyl)-aminocarbonylmethyl]benzoic acid ethyl ester

0.20 g (0.526 m mol) of 4-[(2-(2-piperidino-phenyl)-2-propyl)-aminocarbonylmethyl]benzoic acid and 2 ml of 4N ethanolic hydrochloric acid were stirred at 20°C. After 36 hours, the reaction mixture was evaporated *in vacuo*, and the evaporation residue was distributed between water (at pH = 8 by addition of ammonia (10%)) and ethyl acetate. The organic phase was washed with water, dried, filtered, and evaporated *in vacuo*. The evaporation residue was purified by column chromatography on silica gel (toluene/acetone = 10:1).
Yield: 0.079 g (36.7% of theory),
M.p.: 151–153°C (ether)

Calc.:	C 73.50	H 7.90	N 6.86
Found:	73.40	7.95	6.96

Example 49

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid tert.butyl ester

A mixture of 3.60 g (17.4 m mol) of N,N'-dicyclohexylcarbodiimide, 1.9 ml (20.4 m mol) of tert.butanol and 0.036 g (0.36 m mol) of copper(I)chloride was stirred for 3 days at room temperature, then 12 ml of methylene chloride were added, and the solution thus obtained was added to a solution of 2 g (5.46 m mol) of 4-[(1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid in 80 ml of methylene chloride. After stirring for 16 hours at 20°C, the resultant precipitate was filtered off, washed with methylene chloride, and the methylene chloride solution was evaporated *in vacuo*. The evaporation residue was purified by column chromatography on silica gel (toluene/acetone = 15:1).
Yield: 0.45 g (19.7% of theory),
M.p.: 125–127°C (ether)

Calc.:	C 73.90	H 8.11	N 6.63
Found:	74.20	8.09	6.77

Example 50

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid 2-(nicotinoyloxy)-ethyl ester

A solution of 0.16 g (1.13 m mol) of nicotinic acid chloride in 5 ml of methylene chloride was quickly added to a solution of 0.45 g (1.10 m mol) of 4-[(1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid (2-hydroxy-ethyl)-ester and 0.16 m mol) of triethylamine in 10 ml of methylene chloride. After stirring for 4 hours at 20°C, the reaction mixture was extracted with water, dried, and the methylene chloride solution was filtered and evaporated *in vacuo*. The evaporation residue was purified by column chromatography on silica gel (chloroform/acetone = 3:1).
Yield: 0.34 g (60% of theory),
M.p.: 103–105°C (ether)

Calc.:	C 69.88	H 6.45	N 8.15
Found:	70.13	6.55	8.13

Example 51

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzamide

2.3 g (0.0142 mol) of carbonyl diimidazole were given to 4.76 g (0.013 mol) of 4-[(1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid in 60 ml of absolute pyridine and the mixture was subsequently heated for 45 minutes to 50°C. After cooling in a carbon dioxide/methanol bath 7 ml of liquid ammonia were added and heated for 20 hours to 80°C in an autoclave. Subsequently the reaction mixture was cooled and evaporated *in vacuo*. The residue was dissolved in 50 ml of hot methanol, 200 ml of water were added and the mixture was allowed to rest over-night. The crystalline precipitate was suction filtered and recrystallized from methanol by addition of activated charcoal.
Yi ld: 3.5 g (73.6% of theory),
M.p.: 197–199°C

Calc.:	C 72.30	H 7.45	N 11.50
F und:	72.30	7.45	11.32

Example 52

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]-N-methylbenzamide

2 g (5.46 m m l) of 4-[(1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid and

0.94 g (5.80 m mol) of carbonyl diimidazole in 20 ml f absolut pyridin were h ated to reflux temperature for 1 h ur. Subsequ ntly, 0.41 g (6.07 m mol) f methylamin hydrochloride were added and th mixture was stirred for 1 hour at 20°C and refluxed for 2 h urs. After evaporating *in vacuo,* th residue was distributed between water and m thylen chloride; the organic extract was dried, filt red, and evaporated *in vacuo.* Th evaporation residue was purified by column chromatography on silica gel (chloroform/methanol/conc. ammonia = 10:1:0.05).
Yield: 1.7 g (82% of theory),
M.p.: 218–220°C (isopropanol)

Calc.:	C 72.77	H 7.70	N 11.07
Found:	72.88	7.67	10.91

Analogously to Example 52 the following compound was prepared:

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]-N,N-dimethyl-benzamide
Yield: 52.5% of theory,
M.p.: 148–150°C (ethyl acetate)

Calc.:	C 73.26	H 7.94	N 10.68
Found:	73.60	7.85	10.73

Example 53
4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]-N-butyl-benzamide
0.94 g (5.80 m mol) of carbonyl diimidazole were added to the solution of 2 g (5.46 m mol) of 4-[(1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid in 20 ml of absolute tetrahydrofuran. The mixture was heated to reflux temperature for 30 minutes, 0.44 g (6.1 m mol) of 1-butylamine were added, and the reaction mixture was again refluxed for 2 hours. After evaporating *in vacuo,* the evaporation residue was purified by column chromatography on silica gel (chloroform/acetone:6:1).
Yield: 1.65 g (71.7% of theory),
M.p.: 178–181°C (ethyl acetate)

Calc.:	C 74.09	H 8.37	N 9.97
Found:	74.34	8.26	9.95

Analogously to Example 53 the following compounds were obtained:

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid piperidide
Yield: 73.8% of theory,
M.p.: 131–133°C (toluene)

Calc.:	C 74.79	H 8.14	N 9.69	m/e = 433
Found:	75.13	7.99	9.48	m/e = 433

4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]-benzoic acid morpholide
Yield: 60.5% of theory,
M.p.: 148–150°C (ethyl acetate/ether)

Calc.:	C 71.69	H 7.64	N 9.65
Found:	71.60	7.80	9.57

Example 54
4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzonitrile
1.14 g (6 m mol) of p-toluene-sulfonic acid chloride were added in two portions whilst stirring at room temperature to a mixture of 2.19 g (6 m mol) of 4-[(1-(2-piperidinophenyl)-ethyl)-aminocarbonylmethyl]benzamide and 1.07 g (13.5 m mol) of absolute pyridine. The reaction mixture was stirred for 15 minutes at 20°C and then for 2 hours at 50°C. After cooling, wat r was added, the mixture was adjusted t alkaline by means of conc. ammonia, and extracted thrice with chloroform. The combined chloroform extracts were washed with water, dried ver sodium sulfate, filtered, and evaporated *in vacuo.* The evap ration residue was purified by column chromatography on silica gel (chloroform/ethyl acetate = 4:1).

Yield: 1.15 g (55.3% f the ry),
M.p.: 155–157°C (thyl acetate)

Calc.:	C 76.05	H 7.25	N 12.09
Found:	76.30	7.07	11.90

Example A
Tablets containing 5 mg of 4-[(1-(2-piperidino-phenyl]ethyl)-aminocarbonylmethyl]benzoic acid

Composition:
1 tablet contains:

Active ingredient	(1)	5.0 mg
Corn starch	(2)	62.0 mg
Lactose	(3)	48.0 mg
Polyvinyl pyrrolidone	(4)	4.0 mg
Magnesium stearate	(5)	1.0 mg
		120.0 mg

Method of preparation:
1, 2, 3, and 4 were mixed and moistened with water. The moist mixture was granulated through a screen of mesh size 1.5 mm and dried at approx. 45°C. The dry granulate was granulated through a screen of 1.0 mm mesh size and mixed with 5. The finished mixture was pressed to tablets on a tablets press with punches of 7 mm diameter and an unilateral notch.
Weight of tablet: 120 mg

Example B
Coated tablets containing 2.5 mg of 4-[(1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid

1 coated tablet core contains:

Active ingredient	(1)	2.5 mg
Potato starch	(2)	44.0 mg
Lactose	(3)	30.0 mg
Polyvinyl pyrrolidone	(4)	3.0 mg
Magnesium stearate	(5)	0.5 mg
		80.0 mg

Method of preparation:
1, 2, 3, and 4 were mixed well and moistened with water. The moist mass was granulated through a screen of mesh size 1 mm, dried at approx. 45°C and the granulate was again granulated through the same screen. After adding of 5, curvatured coated tablet cores of a diameter of 6 mm were pressed on a tablets pressing machine. The coated tablet cores thus prepared, were covered in conventional manner with a coating, which essentially consists of sugar and talcum. The finished coated tablets were polished with wax. Weight of coated tablets: 120 mg.

Example C

Tablets containing 10 mg of 4-[(1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid
Composition:
1 tablet contains:

Active ingredient	10.0 mg
Lactose pulverized	70.0 mg
Corn starch	31.0 mg
P lyvinyl pyrrolidon	8.0 mg
Magnesium stearate	1.0 mg
	120.0 mg

Method of preparation:
The mixture f activ ingredient, lactose and corn starch was moistened with a 20% solution f polyvinyl pyrrolidon in water. Th moist mass was granulated through a screen with a mesh siz of 1.5 mm and dried at 45°C. Th dried granulate was granulated through a screen of 1

mm mesh size and homogeneously mixed with magnesium stearate.

Weight of tablets: 120 mg
Punch: 7 mm ϕ with a notch.

Example D
Coated tablets containing 5 mg of 4-[(1-(2-piperidino-phenyl)-ethyl)-aminocarbonylmethyl]benzoic acid

1 coated tablet core contains:

Active ingredient	5.0 mg
Calcium phosphate secondary	70.0 mg
Corn starch	50.0 mg
Polyvinyl pyrrolidone	4.0 mg
Magnesium stearate	1.0 mg
	130.0 mg

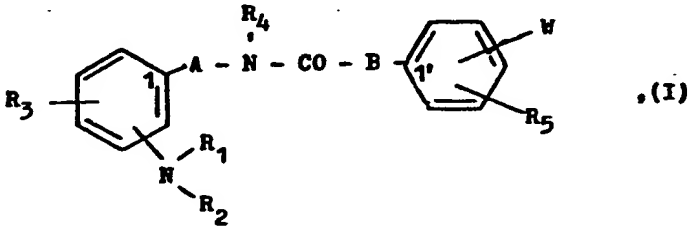
Method of preparation:
The mixture, consisting of the active ingredient, the calcium phosphate and the corn starch, was moistened with a 15% solution of polyvinyl pyrrolidone in water. The moist mass was granulated through a screen of 1 mm mesh size, dried at 45°C and again passed through the same screen. The granulate was mixed with the above mentioned amount of magnesium stearate and the mixture thus obtained was pressed into coated tablet cores.

Weight of core: 130 mg
Punch: 7 mm ϕ

The thus prepared coated tablet cores were covered according to conventional manner with a layer consisting of sugar and talcum. The finished coated tablets were polished with wax.
Weight of coated tablet: 180 mg.

CLAIMS

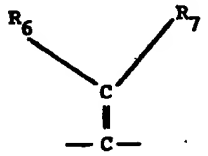
1. Compounds of general formula I



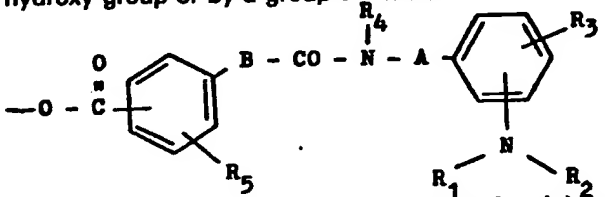
,(I)

[wherein R_1 and R_2, which may be the same or different, each represents an alkyl group containing 1 to 6 carbon atoms or a cycloalkyl group containing 5 to 7 carbon atoms, or R_1 and R_2 together with the nitrogen atom to which they are attached represent an unbranched alkyleneimino group containing 3 to 6 carbon atoms optionally substituted by 1 or 2 alkyl groups, each containing 1 to 3 carbon atoms, or by a hydroxy group and in which a methylene group may optionally be replaced by a carbonyl group, by an oxygen or sulfur atom or by an imino group (which may optionally be substituted by an alkyl group containing 1 to 3 carbon atom, an aralkyl group containing 7 to 10 carbon atoms or by a phenyl or halophenyl group) or an ethylene group may optionally be replaced by an O-phenylene group; and unbranched alkenyleneimino group containing 4 to 6 carbon atoms; a saturated or partly unsaturated azabicycloalkyl group containing 6 to 10 carbon atoms; an aza-1,4-dioxaspiro-alkyl group containing 6 to 8 carbon atoms; or a heptamethyleneimino, octamethyleneimino, nonamethyleneimino or decamethyleneimino group; R_3 represents a hydrogen or halogen atom, a trifluoromethyl, alkyl, hydroxy, alkoxy, alkanoyloxy, mercapto, alkylmercapto, nitro, amino, cyano, alkanoyl, carboxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminosulfonyl, alkylamino, dialkylamino, alkanoylamino, alkoxycarbonylamino or alkylsulfonylamino group (wherein each alkyl part in the above mentioned groups may contain from 1 to 3 carbon atoms), an aralkoxy group containing 7 to 10 carbon atoms or an arylcarbonylamino group; R_4 represents a hydrogen atom or an alkyl group containing 1 to 3 carbon atoms; R_5 represents a hydrogen atom, a halogen atom or an alkyl group containing 1 to 3 carbon atoms; A represents

a bond, a methylene r ethyl ne group optionally substitut d by an alkyl group containing 1 to 5 carbon at ms, a methylene or ethylene group substituted by tw alkyl groups ach containing 1 to 3 carb n atoms, a methylene group substitut d by a cycloalkyl group containing 3 to 7 carbon atoms or by a hydroxyalkyl, alk xyalkyl, cyan , carboxyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aryl or aralkyl group, wherein each of the alkyl parts may contain from 1 to 3 carbon atoms, a cycloalkylidene group containing 3 to 7 carbon atoms or a vinylidene group of formula



wherein R_6 and R_7, which may be the same or different, each represents a hydrogen atom or an alkyl group containing 1 to 3 carbon atoms or one of the radicals R_6 and R_7 represents a cycloalkyl group containing 3 to 7 carbon atoms or an aryl or aralkyl group and the other is as defined above, or R_6 and R_7 together with the carbon atom to which they are attached represent a cycloalkylidene radical containing 5 to 7 carbon atoms; B represents a methylene or ethylene group optionally substituted by an alkyl group 1 to 3 carbon atoms; and W represents a hydrogen or halogen atom, a nitro group, an amino group (optionally substituted by an alkanoyl group containing 1 to 3 carbon atoms) an alkyl group containing 1 to 3 carbon atoms (optionally substituted by a hydroxy or carboxy group or bt one or two alkoxycarbonyl groups containing 2 to 4 carbon atoms each), an alkenyl group containing 2 to 5 carbon atoms substituted by a carboxy or alkoxycarbonyl group containing 2 to 4 carbon atoms, an alkanoyl group containing 1 to 3 carbon atoms, a dialkoxymethyl or trialkoxymethyl group containing 1 to 3 carbon atoms in each alkyl part, an alkylenedioxymethyl group containing 2 or 3 carbon atoms in the alkylene part, a 1,3-oxazoline-2-yl or cyano group, an aminocarbonyl group (optionally substituted by one or two alkyl groups containing 1 to 4 carbon atoms in each alkyl part), an unbranched alkyleneiminocarbonyl group containing 5 to 8 carbon atoms, a morpholinocarbonyl group, a (dialkyldioxolane-yl)-alkoxycarbonyl group containing 7 to 10 carbon atoms or a carboxy group or esterfied carboxy group wherein if the said ester group consists of an alkyl group containing 1 to 6 carbon atoms this may be substituted, in any but the α-position, by a hydroxy, alkoxy, amino, alkylamino, dialkylamino, 1,3-dimethylxanthine-7-yl, alkanolyoxy, aroyloxy, aralkanoyloxy or pyridine-carbonyloxy group or by two hydroxy groups—except in the case of any methyl or methylene group in the above cases, which can only be substituted by one hydroxy group or by a group of formula

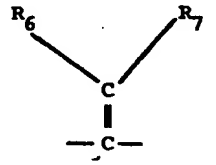


wherein A, B, R_1, R_2, R_3, R_4 and R_5 are as hereinbefore defined whereby each alkyl part of the above alkyl ester substituted may contain from 1 to 3 carbon atoms], and salts thereof.

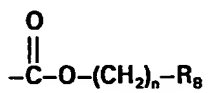
2. Physiologically compatible salts, formed with inorganic or organic acids or bases, of compounds of general formula I as claimed in claim 1.

3. Compounds as claimed in claim 1 or claim 2, wherein R_1 and R_2 together with the nitrogen atom to which they are attached, represent a dialkylamino or N-alkylcyclohexylamino group (wherein each alkyl part may contain from 1 to 4 carbon atoms), an unbranched alkyleneimino group containing 3 to 6 carbon atoms (optionally substituted by one or two methyl groups), a hydroxypiperidino, piperidone-1-yl, tetrahydro-pyridino, morpholino, thiomorpholino, N-methyl-piperazino, N-benzyl-piperzino, N-chlorophenyl-piperazino, heptamethyleneimino or octamethyleneimino group, a saturated or partly unsaturated azabicycloalkyl group containing 7 to 9 carbon atoms, an unbranched alkyleneimino group containing 4 to 6 carbon at ms (wh rein an ethylen gr up is replaced by an o-phenylene group), or a 1,4-dioxa-azaspiroalkyl group containing 7 t 8 carbon atoms; R_3 represents a hydrogen, fluorin , chlorine, bromine, or iodin atom or a methyl, trifluoromethyl, hydroxy, methoxy, benzyoxy, acetoxy, mercapt , methylm rcapto, nitro, amino, dimethylamino, acetylamino, methylsulfonylamino, benzoylamino, ethoxycarbonylamino, cyano, carb xy, methoxycarbonyl, ethoxycarbonyl, aminocarbonyl, acetyl or aminosulfonyl gr up; R_4 repres nts a hydrogen atom or a methyl group; R_5 represents a hydrogen at m, a chlorine atom or a methyl group; A represents a bond, a methylene group optionally substitut d by an alkyl group containing 1 to 3 carbon atoms, a phenyl, cyclohexyl, carboxy, methoxycarbonyl or hydr xymethyl group, a dimethylmethylen ,

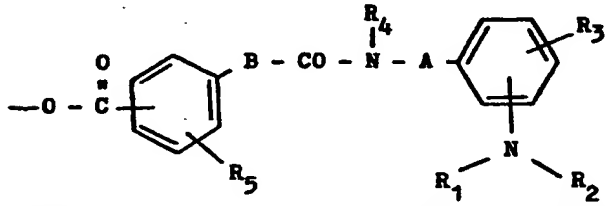
cyclopropyliden or ethylene group r a vinylidene group f formula



wherein R_6 and R_7, which may be the same or different, each represents a hydrogen atom or a methyl group or R_6 and R_7 together with the carbon atom to which they are attached represent a cycloalkylidene radical containing 5 or 6 carbon atoms; B represents a methylene, ethylidene or ethylene group; and W represents a hydrogen atom, a methyl, ethyl, hydroxymethyl, cyano or carboxyvinylene group, an alkyl group containing 1 to 3 carbon atoms substituted by a carboxy group or by one or two alkoxycarbonyl groups containing 2 to 4 carbon atoms each, a carbonyl group (substituted by a hydrogen atom, a methyl, ethyl, hydroxy, alkoxy, (2,2-dimethyldioxolane-4-yl)-methoxy, benzyloxy, pyridylmethyoxy, amino, alkylamino, dialkylamino, piperidino or morpholino group, each alkyl part in the above groups containing from 1 to 3 carbon atoms) or a group of formula

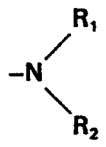


wherein n is 2, 3, or 4, and R_8 represents a hydroxy, methoxy, ethoxy, acetoxy, benzoyloxy, or pyridinecarbonyloxy group, a dialkylamino group containing 1 to 3 carbon atoms in each alkyl part, a 1,3-dimethylxanthine-7-yl group, or a group of formula



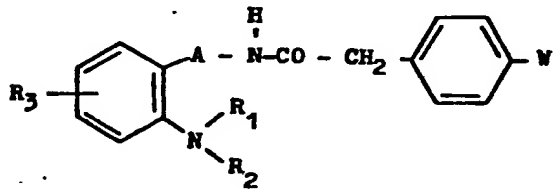
wherein A, B and R_1, R_2, R_3, R_4 and R_5 are as defined above.

4. Compounds as claimed in claim 3, wherein the radical



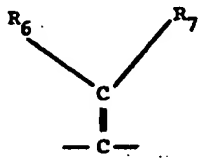
is present in the 2-position and the radical W is present in the 4′-position.

5. Compounds of general formula I a



(Ia)

wherein R_1 and R_2 together with the nitrogen atom to which they are attached, represent a dimethylamino, pyrrolidino, methylpyrrolidino, piperidino, methylpiperidino, dimethylpiperidino, tetrahydro-pyridino, 2-octahydro-isoindolo, or hexamethyleneimino group, R_3 represents a hydrogen, fluorine or chlorine atom or a methyl group, A represents a methylene group (optionally substitut d by a cyclohexyl, phenyl, methoxycarbonyl or ethoxycarbonyl group r an alkyl group containing 1 to 3 carbon atoms), a dimethylmethylene group or a vinylidene group of formula



wherein R_6 and R_7 each represents a hydrogen atom or together with the carbon atom to which they are attached represent a cyclohexylidene group, and W represents a methyl, hydroxymethyl or carboxymethyl group, a carbonyl group (substituted by a hydrogen atom or by a methyl, hydroxy, methoxy, ethoxy, propoxy, isopropoxy, 2-hydroxyethoxy, 2-methoxyethoxy, (2,2-dimethyl-dioxolane-4-yl)-methoxy or 2-diethylaminoethoxy group) and salts thereof.

6. Compounds as claimed in claim 5 wherein R_1 and R_2 together with the nitrogen atom to which they are attached, represent a pyrrolidino, piperidino, methylpiperidino, hexamethyleneimino, tetrahydro-pyridino or 2-octahydro-isoindolo group, R_3 represents a hydrogen, fluorine or chlorine atom or a methyl group, A represents a methylene group (optionally substituted by a methyl, isopropyl, phenyl or methoxycarbonyl group) or a dimethyl-methylene or vinylidene group and W represents a methyl, hydroxymethyl, carboxymethyl, formyl or carboxy group or an alkoxycarbonyl group optionally substituted by a (2,2-dimethyl-dioxolane-4-yl) group, wherein the alkoxy group may contain from 1 to 3 carbon atoms.

7. 4-[(1-(2-Piperidino-phenyl)-ethyl)-aminocarbonylmethyl]-benzoic acid.

8. 4-[(2-Piperidino-benzhydrile)-aminocarbonylmethyl]benzoic acid.

9. C_{1-3} alkyl esters of compounds as claimed in claim 7 or claim 8.

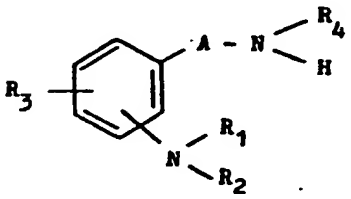
10. Physiologically compatible salts of compounds as claimed in any one of claims 7 to 9 formed with organic or inorganic acids or bases.

11. Compounds as claimed in claim 1 wherein R_1 and R_2, which may be the same or different, each represents an alkyl group containing 1 to 6 carbon atoms or a cycloalkyl group containing 5 to 7 carbon atoms, or R_1 and R_2 together with the nitrogen atom to which they are attached, represent an alkyleneimino group containing 4 to 10 carbon atoms in the alkylene ring (optionally substituted by one or two alkyl groups each containing 1 to 3 carbon atoms), a morpholino or a thiomorpholino group, R_3 represents a hydrogen or a halogen atom, a trifluoromethyl, alkyl, hydroxy, alkoxy, mercapto, alkylmercapto, cyano, nitro, amino, aminocarbonyl, alkylamino, dialkylamino, or alkylsulfonylamino group, whereby each alkyl part in the above mentioned groups may contain from 1 to 3 carbon atoms, A represents a methylene or ethylene group optionally substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, R_4 and R_5 each represent a hydrogen atom, B is as defined in claim 1, and W, which is in the para position, represents a carboxy group and its esters.

12. Compounds as claimed in claim 1 as herein described in ay one of the examples.

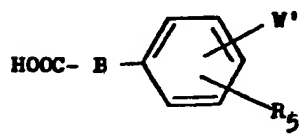
13. Compounds as claimed in claim 11, as herein described in any one of Examples 1, 8, 24, 29–31, 35, 36, 38, 40 or 48.

14. A process for the preparation of compounds as claimed in claim 1, which comprises reacting an amine of general formula II



,(II)

wherein A, R_1, R_2, R_3 and R_4 are as defined in claim 1 (or if A represents one of the above mentioned vinylidene groups one of its tautomers, or a lithium or magnesium-halide complex thereof) with a carboxylic acid of general formula III



,(III)

wherein R_5 and B are as defined in claim 1 and W' represents W as defined in claim 1 or represents a carboxyl group protected by a protective radical, or with reactive derivatives thereof, optionally prepared in the reaction mixture, and if necessary cleaving off a protective radical.

15. A process as claimed in claim 14, wh rein the reacti n is carried in a solvent at temp ratures between −25 and 250°C.

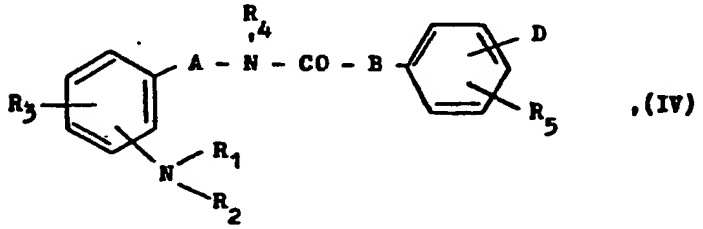
16. A process as claimed in claim 14 or claim 15 wh rein the reacti n is carried ut in the presence of an acid-activating or dehydrating agent.

17. A process as claimed in claim 14 r claim 15 wh rein the reaction is carri d out in the presence of an amine-activating agent.

18. A process as claimed in any one of claims 14 to 17 wherein the reaction is carried out in the presence of an inorganic or tertiary organic base.

19. A process as claimed in any of claims 14 to 18 wherein the water formed during the reaction is removed by azeotropic distillation or by addition of a drying agent.

20. A process for the preparation of compounds of general formula I as claimed in claim 1, wherein W represents a carboxy group, which comprises hydrolytically, thermolytically or hydrogenolytically reacting a compound of general formula IV



,(IV)

wherein R_1, R_2, R_3, R_4, R_5, A and B are as defined in claim 1 and D represents a group being transformable into a carboxy group by means of hydrolysis, thermolysis or hydrogenolysis.

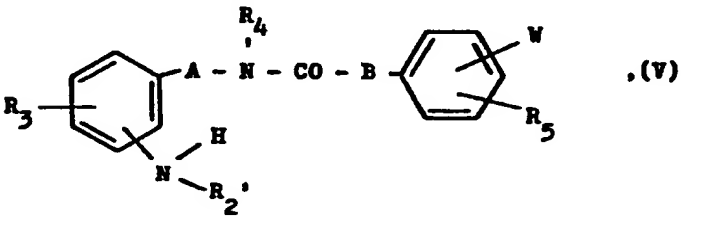
21. A process as claimed in claim 20 wherein the reaction is carried out in a solvent at temperatures between room temperature and the boiling temperature of the reaction mixture.

22. A process as claimed in claim 20 or claim 21 wherein the hydrolysis or thermolysis is carried out in the presence of an acid or base.

23. A process as claimed in claim 20 or claim 21 wherein, if in the compound of formula IV D represents a nitrile or aminocarbonyl group, the reaction is carried out in the presence of a nitrite and an acid.

24. A process as claimed in claim 23 wherein the nitrite is sodium nitrite and the acid is sulfuric acid.

25. A process for the preparation of compounds as claimed in claim 1, which comprises alkylating a compound (optionally formed in the reaction mixture) of general formula V



,(V)

wherein R_3, R_4, R_5, A, B and W are as defined in claim 1 and R_2' represents a hydrogen atom or as defined in claim 1, with a compound of general formula VI

R_1'–E, (VI)

wherein R_1' represents R_1 as defined in claim 1 or together with the radical R_2' in the above compound of formula V represents a straight-chained alkylene group containing 4 to 6 carbon atoms (optionally substituted by one or two alkyl groups containing 1 to 3 carbon atoms) or an n-pentylene group wherein the third methylene group is replaced by an oxygen or sulfur atoms, and E represents a nucleophillically exchangeable group or (if in the radical R_1' a methylene group is replaced by an aldehyde or ketone carbonyl group) a hydrogen atom, if necessary in the presence of a reducing agent and optionally subsequently hydrolyzing.

26. A process as claimed in claim 25 wherein the reaction is carried ut in a solvent at temperatures between 0 and 150°C.

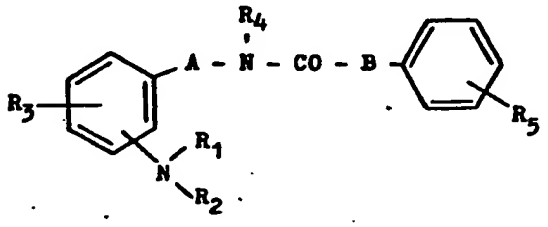
27. A process as claim d in claim 25 or claim 26 wherein th reaction is carried out in the presence of an inorganic r tertiary organic base.

28. A process as claimed in claim 25 or claim 26 wherein the alkylation is carried out with a carbonyl compound in the pres nce of a hydride at pH 7.

29. A process as claimed in claim 28 wherein the hydride is sodium cyanoborohydride.

30. A process as claimed in claim 25 or claim 26 wherein a methylation reaction is carried out using formaldehyde in the presence of formic acid, or hydrogen in the presence of a hydrogenation catalyst.

31. A process for the preparation of compounds of general formula I, wherein W represents a carboxy group, an alkanoyl group, an alkanoyl group containing 1 to 3 carbon atoms or an alkyl group containing 1 to 3 carbon atoms, which comprises reacting a compound of general formula VII



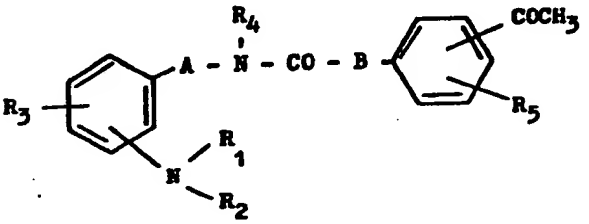
,(VII)

wherein R_1, R_2, R_3, R_4, R_5, A and B are as defined in claim 1, with phosgene, an oxalyl halide, an alkyl or alkanoyl halide containing 1 to 3 carbon atoms each in the alkyl part or with hydrogen cyanide and a hydrogen halide in the presence of a Lewis acid.

32. A process as claimed in claim 31, wherein the reaction is carried out in a solvent at temperatures between 0 and 120°C.

33. A process as claimed in claim 31 or claim 32, wherein the Lewis acid is aluminium chloride.

34. A process for the preparation of compounds of general formula I wherein W represents a carboxy group, which comprises reacting a compound of general formula VIII

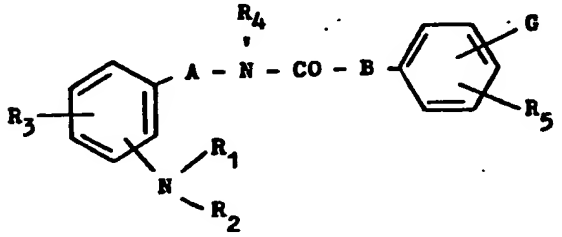


,(VIII)

wherein R_1, R_2, R_3, R_4, R_5, A and B are as defined in claim 1 with a hypohalite (optionally formed in the reaction mixture) in the presence of an alkali base.

35. A process as claimed in claim 34 wherein the reaction is carried out in a solvent at temperatures between 0 and 80°C.

36. A process for the preparation of compounds of general formula I, wherein W represents the carboxy group, which comprises oxidizing a compound of general formula IX

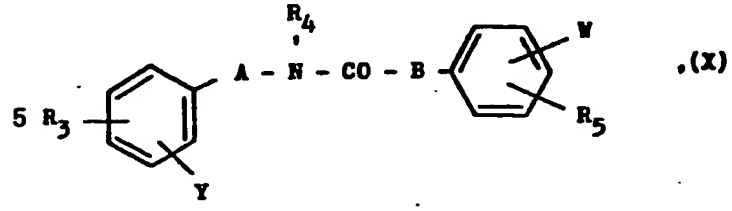


,(IX)

wherein R_1, R_2, R_3, R_4, R_5, A and B are as defined in claim 1 and G represents a group which may be converted into a carboxy group by means of oxidation.

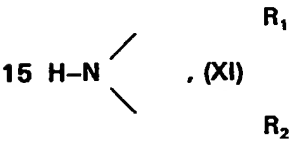
37. A process as claimed in claim 36 wherein the reaction is carried out in a solvent at temperatures between 0 and 100°C.

38. A process for the preparation of compounds of general formula I, wherein R_3 represents a nitro group, which comprises reacting a compound of general formula X



,(X)

wherein R_4, R_5, A, B and W are as defined in claim 1. R_3 represents a nitro group and Y represents a nucleophilically exchangeable radical, with an amine of general formula XI



, (XI)

wherein R_1 and R_2 are as defined in claim 1, and optionally subsequently hydrolyzing.

39. A process as claimed in claim 38, wherein the reaction is carried out in a solvent at temperatures between 20 and 150°C.

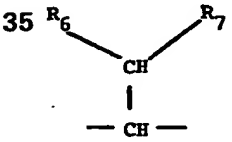
40. A process as claimed in claim 38 or claim 39 wherein the reaction is carried out at the boiling temperature of the reaction mixture.

41. A process as claimed in any one of claims 38 to 40 wherein the reaction is carried out in the presence of an excess of the amine of formula XI and/or the N-formyl derivative thereof.

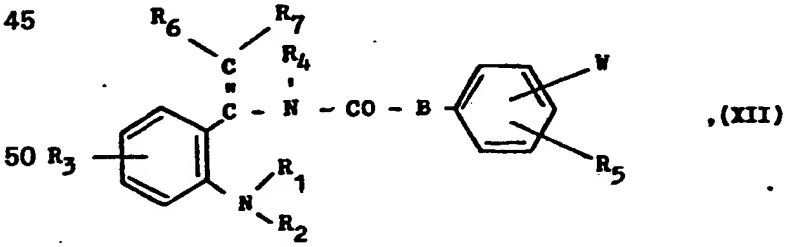
42. A process as claimed in any one of claims 38 to 41 wherein the reaction is carried out in the presence of an inorganic or tertiary organic base and/or a reaction accelerator and/or in a pressure vessel.

43. A process as claimed in claim 42 wherein the reaction accelerator comprises copper or a copper salt.

44. A process for the preparation of compounds of general formula I, wherein A represents a group of formula



wherein R_6 and R_7 are as defined in claim 1, which comprises reducing a compound of general formula XII



,(XII)

wherein R_1, R_2, R_3, R_4, R_5 R_6, R_7, B and W are as defined in claim 1, with hydrogen in the presence of a hydrogenation catalyst.

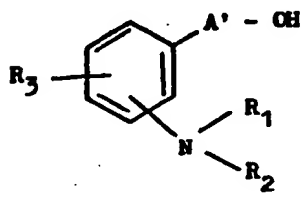
45. A process as claimed in claim 44 wherein the reaction is carried out in a solvent.

46. A process as claimed in claim 44 or claim 45 wherein the reaction is carried out at a hydrogen pressure of 1 to 5 bar.

47. A process as claimed in any of claims 44 to 46 wherein the reaction is carried out at temperatures between 0 and 100°C.

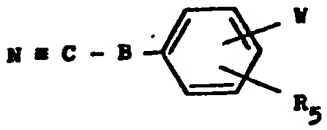
48. A process for the preparation of compounds of general formula I, [wherein R_4 represents a hydrogen atom and A represents a methylene or ethylene group (optionally substituted by an alkyl group containing 1 to 5 carbon atoms), a methylene or ethylene group substituted by two alkyl groups containing 1 to 3 carbon atoms each, a methylene group (substituted by a

cycloalkyl gr up containing 3 t 7 carbon atoms, an alk xyalkyl, carboxyl, alkoxycarbonyl, aryl or aralkyl group, whereby each of the above mention d alkyl parts may contain from 1 to 3 carbon atoms), or a cycloalkyliden gr up c ntaining 4 to 7 carbon atoms] which comprises, reacting a compound of general formula XIII



,(XIII)

wherein R_1, R_2 and R_3 are as defined in claim 1, and A' represents a methylene or ethylene group (optionally substituted by an alkyl group containing 1 to 5 carbon atoms), a methylene or ethylene group substituted by two alkyl groups containing 1 to 3 carbon atoms each, a methylene group (substituted by a cycloalkyl group containing 3 to 7 carbon atoms, or an alkoxyalkyl, carboxyl, alkoxycarbonyl, aryl or aralkyl group, whereby each of the aforementioned alkyl parts may contain from 1 to 3 carbon atoms), or a cycloalkylidene group containing 4 to 7 carbon atoms, with a compound of general formula XIV,



,(XIV)

wherein R_5, B and W are as defined in claim 1, in the presence of a strong acid.

49. A process as claimed in claim 48, wherein the strong acid is sulfuric acid.

50. A process as claimed in claim 48 or claim 49, wherein the reaction is carried out in a solvent at temperatures between 20 and 150°C.

51. A process as claimed in any one of claims 14 to 50 wherein a compound of formula I wherein W represents a carboxy group, initially obtained, is converted by means of esterification or amidation into an ester of amide derivative thereof.

52. A process as claimed in any one of claims 14 to 50 wherein a compound of formula I, wherein R_3 and/or W represent nitro groups, initially obtained, is reduced to a compound of formula I wherein R_3 and/or W represent amino groups.

53. A process as claimed in any one of claims 14 to 50 wherein a compound of formula I initially obtained, wherein R_3 and/or W represent an amino group, is converted via a diazonium salt into a compound of formula I wherein R_3 represents a hydrogen or a halogen atom, a hydroxy, alkoxy, mercapto, alkylmercapto, chlorosulfonyl or cyano group and/or W represents a hydrogen or a halogen atom or a cyano group.

54. A process as claimed in claim 53 wherein, a compound of formula A wherein R_3 represents a hydroxy group thereby obtained is alkylated to yield a compound of formula I wherein R_3 represents an alkoxy group.

55. A process as claimed in claim 53 wherein a compound of formula I wherein R_3 represents a chlorosulfonyl group thereby obtained is converted by means of ammonia to a compound of formula I wherein R_3 represent an aminosulfonyl group.

56. A process as claimed in any one of claims 14 to 50 wherein a compound of formula I initially obtained wherein R_3 represents an amino group is acylated to yield a compound of formula I wherein R_3 represents an alkanoylamino, aroylamino, alkoxycarbonylamino or alkylsulfonylamino group.

57. A process as claimed in any one of claims 14 to 50 wherein a compound of formula I initially obtained wherein R_3 represents an amino group, group is converted by alkylation to a compound of formula I wherein R_3 represents an alkyl- or dialkylamino group.

58. A process as claimed in any one of claims 14 to 50 wherein a compound of formula I initially btained wh rein R_3 r presents a chlorine or a bromine atom is converted by dehalogentation to a compound f formula I wherein R_3 represents a hydrogen atom.

59. A process as claimed in any one of claims 14 to 50 wherein a compound of formula I initially obtained wherein R_3 represents a nitril group is converted by hydr lysis or alcoholysis to a compound of formula I wherein R_3 represents an aminocarbonyl, carboxycarbonyl or alk xycarbonyl group.

60. A process as claimed in any on of claims 14 to 50 wherein a compound of formula I initially obtained wherein R_3 represents a carboxycarbonyl or alk xycarbonyl group and/or W represents a carboxy r sterified carboxy group, is reduced to a compound f formula I wherein

R_3 and/or W represents a formyl or hydroxymethyl group.

61. A process as claimed in any one of claims 14 to 50 wherein a compound of formula I initially obtained, wherein W represents an alkoxycarbonyl group (wherein the alkoxy group may contain from 2 to 6 carbon atoms) substituted in any but the α-position by a hydroxy group, is acylated to a compound of formula I wherein W represents an acyloxy group.

62. A process as claimed in any one of claims 14 to 50 wherein a compound of formula I initially obtained, wherein W represents a hydroxymethyl group, is halogenated and then reacted with a malonic acid diester to form a compound of formula I wherein W represents an ethyl group substituted by two alkoxycarbonyl groups.

63. A process as claimed in any one of claims 14 to 50 wherein a compound of formula I initially obtained, wherein W represents a formyl group, is converted by means of condensation and optional subsequent hydrolysis and/or decarboxylation to a compound of formula I wherein W represents a vinyl group substituted by a hydroxycarbonyl or alkoxycarbonyl group.

64. A process as claimed in any one of claims 14 to 50 wherein a compound of formula I initially obtained, wherein W represents an ethyl group substituted by two alkoxycarbonyl groups, is converted by hydrolysis and decarboxylation to a compound of formula I wherein W represents an ethyl group substituted by one carboxy group.

65. A process as claimed in any one of claims 14 to 50 wherein a compound of formula I initially obtained, wherein W represents a carboxy group, is converted via a sulfonic acid hydrazide and subsequent disproportionation into a compound of formula I wherein W represents a formyl group.

66. A process as claimed in any one of claims 14 to 50 wherein a compound of formula I initially obtained, wherein R_1 and R_2 together with the nitrogen atom to which they are attached represent an aza-1,4-dioxa-spiro-alkyl group containing 6 to 8 carbon atoms, is hydrolysed to a compound of formula I wherein R_1 and R_2 together with the nitrogen atom to which they are attached represent an unbranched alkyleneimino group containing 4 to 6 carbon atoms wherein a methylene group is replaced by a carbonyl group.

67. A process as claimed in any one of claims 14 to 50 wherein a compound of formula I initially obtained, wherein R_1 and R_2 together with the nitrogen atom to which they are attached represent an unbranched alkyleneimino group containing 4 to 6 carbon atoms wherein a methylene group is replaced by a carbonyl group, is reduced to a corresponding hydroxy-alkyleneimino compound of formula I.

68. A process as claimed in any one of claims 14 to 50 wherein a compound of formula I initially obtained, wherein W represents an aminocarbonyl group, is dehydrated to a compound of formula I wherein W represents a cyano group.

69. A process as claimed in any one of claims 14 to 68 wherein a compound of formula I initially obtained is subsequently converted into a salt thereof with an organic or inorganic acid or base, or a salt of a compound of formula I initially obtained is subsequently converted into a compound of formula I.

70. A process as claimed in any one of claims 14 to 69 for the preparation of compounds as claimed in claim 11.

71. A process for the preparation of compounds as claimed in claim 1 substantially as herein described in any one of the Examples.

72. A process for the preparation of compounds as claimed in claim 11 substantially as herein described in any one of Examples 1, 8, 24, 29–31, 35, 36, 38, 40 or 48.

73. Compounds as claimed in claim 1 when prepared by a process as claimed in any one of claims 14 to 72.

74. Compounds as claimed in claim 11 when prepared by a process as claimed in claim 70 or claim 72.

75. Pharmaceutical compositions comprising as active ingredient at least one compound of formula I as defined in claim 1 or a physiologically compatible salt thereof, in association with one or more pharmaceutical carriers or excipients.

76. Compositions as claimed in claim 75 in a form suitable for oral or parenteral administration.

77. Compositions as claimed in claim 75 or claim 76 in the form of tablets, coated tablets, capsules, powders or suspensions.

78. Compositions as claimed in any one of claims 75 to 77 in the form of dosage units.

79. Compositions as claimed in claim 78 wherein each dosage unit contains from 1 to 50 mg of active ingredient.

80. Compositions as claimed in claim 79 wherein each dosage unit contains from 2.5 to 20 mg of active ingredient.

81. Compositions as claimed in any one of claims 75 to 80 wherein the compound of formula I is as defined in claim 11.

82. Pharmaceutical compositions as claimed in claim 75 substantially as herein described.

83. Pharmaceutical compositions substantially as herein described in any one of Examples A

to D.

84. Compounds of general formula I as claim d in claim 1 and physiologicalyl compatible salts th reof for use in a method f tr atment f patients suffering from disorders of intermediary metabolism and/or blood sugar dis rders.

85. A method of treating patients suffering from, or susceptible to disorders of intermediary metabolism and/or blood sugar disorders which comprises administering to the said patient an effective amount of a compound of formula I as defined in claim 1 or a physiologically compatible salt thereof.

86. Each and every novel method, process, compound or composition herein disclosed.

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